STUDY PROTOCOL

NCT03459079

Protocol identification: lanifibranor/2018

IRB number:

Version 2.5 – February 6, 2022

Study title

Efficacy, Safety and Mechanism of Action of Lanifibranor (IVA337) in Patients with Type 2 Diabetes (T2DM) and Nonalcoholic Fatty Liver Disease (NAFLD)

Investigational medicinal product: IVA337 (lanifibranor)

Development Phase: II. Investigator Initiated study
Study initiation date: Q1 2018
Study completion date (expected): Q2 2020

Principal Investigator: Kenneth Cusi, M.D., F.A.C.P., F.A.C.E
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Signature page

Study title: Efficacy, Safety and Mechanism of Action of Lanifibranor (IVA337) in Patients with Type 2 Diabetes (T2DM) and Nonalcoholic Fatty Liver Disease (NAFLD)

Study code: lanifibranor/2018

Principal Investigator and co-Investigators have approved the protocol Version 2.4.3 October 18, 2021 and confirm hereby to perform this study in compliance with this protocol, the current Helsinki Declaration (Appendix A), GCP and applicable regulatory requirements.

INVESTIGATORS		
Kenneth Cusi, M.D., F.A.C.P., F.A.C.E Professor of Medicine Principal Investigator	Date:	Signature :
Other Investigators: Diana Barb, M.D. Romina Lomonaco, M.D. Eddison Godinez Leiva, MD.	Date :	Signature:

Revision history

Version 2.5 February 7th, 2022; Main Revision summary: change related to concomitant medications further to new information provided in updated IB version 12. Change of pharmacovigilance contractor. Included results of the NATIVE study published in the New England Journal of Medicine October 21, 2021.

Version 2.4.3 October 18, 2021; Main Revision summary: updated information on Investigational Product and updated main representative for Inventiva S.A.

Version 2.4.2(b) May 4, 2021; Main Revision summary: updated list of investigators and DSMB (Dr. J.M. Muñoz Peña replacing Dr. A. Bianchi); updated research coordinator (Chrystal Bailey replacing Danielle Poulton).

Version 2.4.1. Statistical analysis modified (number of patients reduced based on the results from NATIVE on steatosis [primary endpoint in this trial])

2.0. June 12, 2018: Incorporation of FDA and IRB requirements including those related to Eligibility Criteria, Stopping Criteria and Safety Monitoring

1.0 - February 10, 2018 Initial

Synopsis

Study title: Efficacy, Safety and Mechanism of Action of lanifibranor (IVA337) in Patients with Type 2 Diabetes (T2DM) and Nonalcoholic Fatty Liver Disease (NAFLD).

Study code: Lanifibranor / 2018

Trial registration: NCT number

Protocol version and date: Version 2.3, November 27

Development Phase: II, Investigator Initiated study

Investigators & study location:

Principal Investigator: Kenneth Cusi, M.D., F.A.C.P., F.A.C.E

Chief, Division of Endocrinology, Diabetes and Metabolism

The University of Florida

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P.O. Box: 100226

Gainesville, FL 32610-0226

Studied period: First enrolment: Q3 2018. Expected completion date: Q4 2020.

Objectives: The primary aim is to establish the safety, efficacy and mechanism of action of lanifibranor in patients with Type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD). Specifically, to determine if lanifibranor decreases intrahepatic triglycerides (IHTG) (primary endpoint), improves hepatic insulin sensitivity, endogenous (hepatic) glucose production, gluconeogenesis and de novo lipogenesis (DNL). This will be achieved by using a combination of intravenously infused stable isotopes and with the infusion of a low- and high-dose insulin infusion during a euglycemic hyperinsulinemic clamp with indirect calorimetry. In addition, exploratory analysis with surrogate plasma biomarkers and imaging on liver fibrosis changes on with treatment will be performed.

Study design: The study is a two arm (placebo, lanifibranor 800 mg/day), randomized (1:1), double-blind, placebo-controlled, 24-week treatment study. There is in addition a non-obese subject control group for the metabolic and imaging procedures.

Study duration: The total time (from first patient enrolled to last patient finished) will be 32±4 weeks (4-6 weeks for run-in, 24 weeks of treatment and 4 weeks post-study follow-up), with an estimated recruitment period of 6-9 months.

Total number of subjects: 34 randomized to study drug or placebo. Ten healthy non-obese will also be studied as "normal controls" for all the metabolic and imaging tests to be performed.

Diagnosis and main criteria for inclusion:

1. Be able to communicate meaningfully with the investigator and legally competent to provide written informed consent
2. Have an age between 21 to 75 years inclusive
3. Subjects should be on stable standard of care and background therapy for ongoing chronic conditions, including stable doses of anti-diabetic medications, for at least two (2) months prior to trial entry
4. Have uncontrolled diabetes with a fasting plasma glucose (FPG) ≥ 100 mg/dL but ≤ 250 mg/dL and HbA1c ≥ 6.0% but ≤ 9.5%, on diet alone, or on metformin (≥1,000 mg/day), and/or sulfonylurea and/or DPP-IV therapy, SGLT2 inhibitors or GLP1RA. These medicines will be continued at stable doses during the entire study.
    a. Subjects with an HbA1c > 8.0% but ≤ 9.5% will have their metformin (minimum dose required: 1,000 mg/day) maximized to 1,000 mg BID and/or

glimepiride 2 mg once daily added during the first 2 weeks of the run-in period. The baseline visit to initiate lanifibranor (V4; Time 0 or randomization visit) will be not sooner than 8 weeks from diabetes medication titration and the patient should have an HbA1c ≤9.0% to proceed to randomization (V4).

b. In addition, if both metformin and glimepiride (or another sulfonylurea) are already maximized at study entry (or the patient is intolerant to either) and the HbA1c ≥ 9.0% but ≤9.5%, we will add sitagliptin 100 mg daily (or an equivalent dose of another DPP-IV inhibitor) to reach an HbA1c ≤9.0% to proceed to randomization (V4).

5. Presence of hepatic steatosis (Intrahepatic Triglycerides IHTG) > 10 % determined by Magnetic Resonance and Spectroscopy (1H-MRS).
6. Have no new symptoms associated with decompensated diabetes in the previous 3 months.
7. Compensated liver disease with the following hematologic and biochemical criteria on entry into protocol:
    - Hemoglobin > 11 g/dL for females and > 12 g/dL for males
    - White blood cell (WBC) > 2.5 K/μL
    - Neutrophil count > 1.5 K/μL
    - Total bilirubin ≤ 1.3 mg/dL (≤ 22.2 μmol/L). Patients with bilirubin ≤ 1.3 mg/dL can be included if non-conjugated bilirubin in the setting of a Gilbert's syndrome.
    - Albumin > 36 g/L
8. No other causes of chronic liver disease (autoimmune, primary biliary cholangitis, HBV, HCV, Wilson's, α-1-antitrypsin deficiency, hemochromatosis, other).
9. Negative pregnancy test or at least two-year post-menopausal. Women with childbearing potential (i.e. fertile, following menarche and until becoming post- menopausal unless permanently sterile) must be using a highly effective method of contraception (i.e. combined (estrogen and progesterone containing) hormonal/ progesterone-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner). The contraceptive method will have to be followed for at least one menstruation cycle after the end of the study.

Exclusion criteria:

1. Evidence of liver disease other than NAFLD.
2. History of excessive alcohol intake, defined by ≥ 21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to enrollment, where a "unit" of alcohol is equivalent to 12-ounce beer, 4-ounce glass of wine, or 1 ounce shot of hard liquor.
3. Unstable metabolic condition: Weight change > 5 kg in the 3 months prior to enrollment, diabetes with poor glycemic control (HgbA1c > 9.5% or FPG > 250 mg/dl), introduction of an anti-obesity drug/malabsorptive or restrictive bariatric (weight loss) surgery in the past 6 months prior to screening.
4. History of gastrointestinal malabsorptive bariatric surgery within less than 5 years or ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months.
5. Subjects on sulfonylureas, metformin, GLP-1RA or DPP-IV unless the dose and body weight (within 5%) have been stable for at least two (2) months prior to study entry.
6. Patients on insulin, pioglitazone (or prior use in the past 12 months).

7. Patients on any of the following medications unless the patient has been on stable doses of such agents for the past two (2) months before entry into the study: thiazide or furosemide diuretics, beta- blockers, or other chronic medications with known adverse effects on glucose tolerance levels. Patients may be taking stable doses of estrogens or other hormonal replacement therapy if the patient has been on these agents for the prior two (2) months. Patients taking systemic glucocorticoids will be excluded.

   Treatment with strong inducers or inhibitors of CYP2C8, or treatment with substrates of CYP2B6 or CYP2C8. When administered chronically, they should be replaced 2 months before trial entry (See Inclusion criterion #3). If not administered chronically, they should be stopped at least 7 days before first dosing.

8. Patients with:
   a. History of myopathies or evidence of active muscle diseases
   b. Unstable cardiovascular disease, including:
      i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months
      ii. History of (within prior 3 months) or current unstable cardiac dysrhythmias
      iii. Uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg.
      iv. Stroke or transient ischemic attack within the prior 6 months
   c. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer
   d. History of bladder disease and/or hematuria or has current hematuria unless due to a urinary tract infection
   e. Any of the following laboratory values:
      ii. Serum bilirubin > 1.3 mg/dL (or > 22.2 µmol/L). Patients with bilirubin > 1.3 mg/dL can be included if non-conjugated bilirubin in the setting of a Gilbert's syndrome.
      iii. Serum ALT > 3X ULN
      iv. INR > 1.2
      v. Platelets < 150,000 per microliter of blood
      vi. Renal impairment as demonstrated by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m2
      vii. Total creatinine kinase > 1.5 X ULN
      viii. Lipase > 1.3X ULN or >2.0X ULN if on a DPP-IV inhibitor. *(if abnormal values are confirmed when repeated within 3 weeks)
      ix. Hemoglobin A1c > 9.5%

9. Significant systemic or major illnesses other than liver disease, including those listed in exclusion criteria #8 and pulmonary disease, organ transplantation, serious psychiatric disease, that, in the opinion of the investigator, would preclude treatment with lanifibranor and/or adequate follow up.

10. HB antigen > 0, HCV > 0 (patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years), prior history of HIV infection.

11. Pregnancy/lactation or inability to adhere to adequate contraception in women of child-bearing potential.

12. Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study.
13. Body mass index (BMI) > 45 kg/m2.
14. Type 1 diabetes and type 2 diabetic patient on insulin.
15. Diabetic ketoacidosis.
16. Fasting plasma triglycerides > 500 mg/dL.
17. Hemostasis disorders or current treatment with anticoagulants.
18. Participation in any other investigational drug study within the previous 3 months.
19. Have a known hypersensitivity to any of the ingredients or excipients of the IMP including: Lactose monohydrate, hypromellose, sodium lauryl sulphate, sodium starch glycolate, magnesium stearate, Opadry™ II 85F18422, DSS Granular, cellulose microcrystalline, maize starch.
20. Be possibly dependent on the Investigator (e.g., including, but not limited to, affiliated employee).
21. Osteopenia or any other well documented bone disease. Patient without well documented osteopenia treated with vitamin D and/or calcium based supplements for preventive reasons can be included.
22. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of investigator.
23. Metallic implant of any sort that prevents MRI examination including, but not limited to: aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, tattoo, body piercing that cannot be removed, cochlear implant; or any other contraindication to MRI examination.

Test product, dose and mode of administration:

Tablets of lanifibranor 400 mg or placebo, 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.

Prohibited concomitant medications:

- PPAR gamma agonists, PPAR Alpha agonists (fibrates), ezetimibe,
- Bile salts chelators, phytosterols, fish oils,
- Insulin,
- Vitamins E (alpha-tocopherol),
- Anticoagulants (incl. warfarin, dabigatran, rivaroxaban, apixaban),
- Systemic steroids (more than physiological replacement of 30 mg of hydrocortisone per day).
- Substrates of CYP2B6 (e.g. artemether, artemisinin, bupropion, coumarins [e.g. warfarin, acenocumarol], cyclophosphamide, efavirenz, ifosfamine, mephobarbital, methadone, nevirapine, pethidine, propofol, selegiline). However, if medically necessary, these treatments can be administered for a single intake, occasionally.
- Substrates of CYP2C8 (e.g. amodiaquine, clopidogrel, daprodustat, dasabuvir, enzalumatide, montelukast, paclitaxel, repaglinide, torasemide). However, if medically necessary, these treatments can be administered for a single intake, occasionally.
- CYP2C8 strong inducers (e.g. pentobarbital, phenytoin, rifampin, rifamycin, secobarbital). However, if medically necessary, these treatments can be administered for a single intake,

occasionally.

- CYP2C8 strong inhibitors, when systemically administered, i.e. by oral, intra-venous or intra-muscular route of administration (e.g. gemfibrozil, clopidogrel, felodipine, zafirlukast, candesartan celixetil, ketoconazole).

Allowable medications for standard care or precautions:

- ***Obesity***: stable weight defined by no more than a change of 5 kg (see exclusion criteria N° 3).
- Treatment used for the underlying medical condition

  Treatments are allowed within certain restrictions (described above and below) and provided that they have been kept at ***stable doses for at least 2 months before inclusion in the study***.
  - Type 2 diabetes:
    - Metformin,
    - Sulfonylureas,
    - Dipeptidyl peptidase-4 inhibitors,
    - Sodium-glucose transport protein 2 inhibitors: canagliflozin, dapagliflozin and empagliflozin.
    - GLP-1RA
  - ***Hyperlipidemia***: only statins at stable doses will be allowed.
  - ***Antiplatelets agents:*** The antiplatelets agents (incl. low-dose aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor) are allowed.
  - ***Herbal supplements:*** Herbal preparations or vitamin supplements should not be taken as it is difficult to know exactly what they contain and could be liver toxic.

If a symptomatic medication is needed to treat adverse events that may be related to IMP, the investigator will inform the Principal Investigator about the concomitant medication given.

Duration of treatment: lanifibranor or placebo to match will be given for 24 weeks.

Parameters assessed during the study*:* Continuous recording of adverse events and concomitants therapies, physical examination, vital signs, ECG (12-leads), hematology, blood biochemistry and urinalysis, liver enzymes, oral glucose tolerance test, exploratory biomarkers adiponectin, ProC3, CK-18, genotyping.

Imaging such as fibroscan, liver fibrosis, liver IHTG and T1 MR mapping.

All patients, insulin sensitivity study: 2-step insulin clamp with glucose turnover measurements.

Primary efficacy criterion. Determine if lanifibranor decreases intrahepatic triglycerides (IHTG) (primary endpoint), improves hepatic insulin sensitivity, endogenous (hepatic) glucose production, gluconeogenesis and de novo lipogenesis (DNL).

Statistical methods and Safety:

Sample size*:* based on the most recent studies, patients with NAFLD are expected to have a mean baseline IHTG of approximately 15%. The earlier power calculations were based on results with pioglitazone from a 6-month study (1) and a more recent 18-month RCT (2) but they wee revised in version 2.4.1 of the protocol based on the results with lanifibranor 800 mg/day (same dose as this study) from a 6-month RCT (NATIVE) that used liver biopsy (histology) as the primary endpoint (provided in detail by Inventiva to the PI Dr. Cusi). In NATIVE, the proportion of patients with a reduction in steatosis to lanifibranor was 73% versus 26% with placebo (steatosis being the primary endpoint of this study); being greater than with pioglitazone in the 6-month Belfort et al study

[1]). Based on these results, this would translate to liver fat imaging on ^{1}H-MRS of a relative reduction of fat liver with lanifibranor to be ≥50% compared to placebo. This represents a change of ≥7.0% with lanifibranor versus the control group. The expected standard deviation of the change from baseline is expected to be 7%. Considering a type I error of 0.05 (2- sided), a power of 0.80, an allocation ratio of 1:1, the same variance in both treatment groups and a parametric test of mean comparison, the required sample size per group is 15 patients to complete treatment. Assuming that 10 % of randomized patients will not complete the trial, the total number of patients to be randomized is 33-34 patients. Considering a type I error of 0.05 (2-sided), a power of 0.80, an allocation ratio of 1:1, the same variance in both treatment groups and a parametric test of mean comparison the required sample size per group is 15 patients. Assuming that 10 % of randomized patients will not complete the trial, the total number of patients to be randomized is 34.

Randomization*:* Patients will be randomized equally 1:1: to either dose of lanifibranor or placebo. The randomization list will be setup with blocs of size equal to 4.

Safety variables*:* The review of safety and tolerance will be performed on the safety population. The safety analysis will be based on the reported AEs and other safety information. The Principal Investigator will use its most updated list of potentially clinically significant abnormalities (PCSA) in clinical laboratory tests, vital signs, and ECG for the final analysis. The effect of the demographic differences (gender, age, etc.) and risk factors of clinical relevance will be explored.

Efficacy variables:

Primary outcome: Change in IHTG quantified by ^{1}H-MRS from baseline to 24 weeks

Secondary endpoints:

The following changes from baseline to 24 weeks of treatment will be evaluated:

- Proportion of responders defined as the percentage of patients reaching a decrease from baseline in IHTG (quantified by ^{1}H-MRS) to week 24 of ≥ 30%. The definition of "responders" as those with a ≥ 30% reduction in liver fat by ^{1}H-MRS is empiric as there are no studies (except the Belfort et al, NEJM 2006 (1) and Cusi et al (2) with pioglitazone) comparing simultaneously ^{1}H-MRS data with liver histology, but it is assumed that such threshold is likely to correlate with positive histological changes in NASH, based on the investigator's experience.
- Proportion of patients with NAFLD resolution considered as having ≤ 5.5% IHTG (quantified by 1H- MRS) at 24 weeks.
- Changes in hepatic fibrosis measured by several techniques:
  a) Vibration-controlled transient elastography (Fibroscan) (3);
  b) Two-dimensional magnetic resonance elastography (2D-MRE) (4); and
  c) A novel T1 MRI mapping scanning protocol that allows for the accurate non-invasive measurement of liver fibrosis, in collaboration with the Oxford laboratory (5).
- Change in plasma biomarkers of liver fibrosis (i.e., cytokeratin CK-18, proC3) or clinical laboratories.
- Change in metabolic outcomes standard for such pilot trials (see ref. 1, 2, and 6) at week 24 of treatment, and will include:
  - Determination of hepatic insulin sensitivity
  - De novo lipogenesis
  - Glycemic control: HbA1c,
  - Advanced lipid testing.

Study procedures:

All patients will undergo ten visits, screening V1 to V3 (-6 weeks to -1 week), randomization V4

(time 0), follow-up V5 (week 4), follow-up V6 (week 8), follow-up V7 (week 12), follow-up V8 (week 16), follow-up V9 (week 20), repeated baseline studies at V10 (week 23), V11 (week 24), and off-drug follow-up V12 (week 28). For all visits time windows are defined up to +/- 5 days compared to V1 and are indicated in the Table 1.

Patients will be randomized to either dose of lanifibranor or placebo at V4 and treated for 24 weeks until V11. Please note that due to COVID-19 pandemic, in order to be able to accommodate important follow-up study procedures, for some of the already enrolled subjects, treatment with lanifibranor may have to be extended by 1-8 weeks. This time frame will allow completion of the follow-up liver MRI (V10) and perform the insulin clamp (V11). These are essential procedures in order to obtain the primary and secondary outcomes of the study.

A vital signs, weight, height and waist measurements will be performed at each visit. An ECG will be done at screening (V1) and at end of treatment (V11). A physical exam including weight measurement every 4 weeks once patients randomized to study medication. Adverse events and concomitant medications will be recorded throughout the study. Patients and caregivers will be educated for potential symptoms of adverse effects that should be reported to the investigators, such as skeletal muscle pain, weight gain, peripheral edema, shortness of breath, etc. If a patient has symptoms of dyspnea, edema, or a presumptive diagnosis of heart failure, NT-proBNP should be measured as close to the event as possible. The potential for hypoglycemia will be monitored carefully, particularly in patients on anti-diabetic medications, as detailed in the protocol.

The routine laboratory assessments performed at V1, V4, V5, V6, V7, V8, V9 V11 and V12 will include: complete blood count, comprehensive metabolic profile and lipids. CK and CK-MB will be measured every 4 weeks once the patient is randomized to study medication.

Urine Samples will be collected at V1, V11 and at V12.

Urine pregnancy test will be performed at V1, V4, V7, V9, V11 and V12.

Figure 1. Study Design

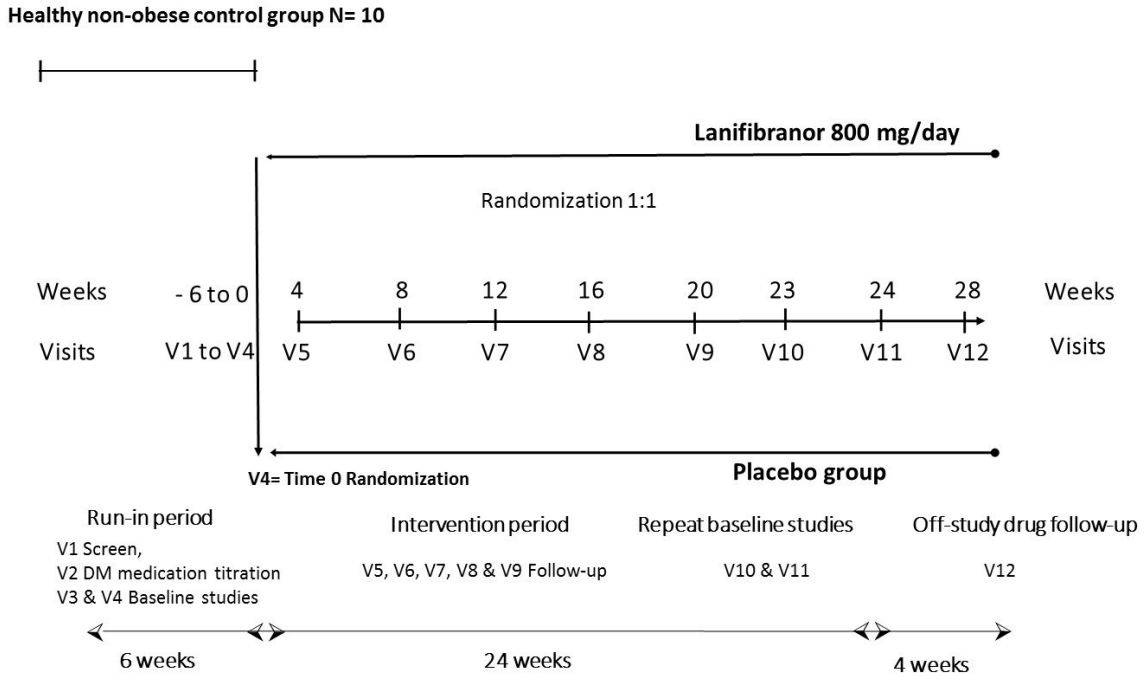


Table 1. Study Schedule of procedures

Inventiva Study	n = 34 patients with T2DM and 10 healthy non-obese controls (controls only to undergo OGTT and euglycemic insulin clamp)											
Principal Investigator: Kenneth Cusi, MD												
Institution: University of Florida												
		Run-in period										
Study Period	**Screen**	**DM med titration**								**Repeat baseline studies**		**Follow-up**
VISIT	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
Study Day (+/- 5 days)	**-42**	**-28**	**-7**	**-7 and 0**	**28**	**56**	**84**	**112**	**140**	**161**	**167 and 168**	**196**
Weeks	-6	-4	-1	Time 0 Randomization	4	8	12	16	20	23	23 to 24	28
Key procedure per visit	Screen + fibroscan	Medication titration	Liver imaging	Ins. sensitivity, DNL, GNG	follow-up	follow-up	follow-up	follow-up	follow-up	Liver imaging	Ins. sensitivity, DNL, GNG	off-drug f/u
Procedure												
Sign informed consent form	X											
Review Eligibility (inclusion/exclusion criteria)	X											
Medical History	X										X	
Concomitant medications	X			X	X	X	X	X	X	X	X	X
Alcohol screen (AUDIT questionnaire)	X										X	
Drug screen	X											
Serology: HIV, HB antigen, HCV PCR, ferritin*	X											
Physical Exam	X				X	X	X	X	X	X	X	X
Vital Signs, Weight/Ht, waist measurement	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X										X	
† Routine Chems (CBC, CMP, lipids, CPK, CPK-MB, serum creatinine, eGFR, lipase)	X			X	X	X	X	X	X			X
Hemoglobin A1c	X		X #	X		X		X			X	X
TSH, free T4*	X											
Urinalysis	X										X	X
Urine pregnancy test	X			X			X		X		X	X
FSH (postmenopausal patients only)	X											
STAFF ASSESSMENTS												
Outpatient nursing staff assessment	X			X	X		X		X		X	X
Study Coordinator assessment	X	X	X	X	X		X		X	X	X	X
Physician assessment	X			X	X		X		X		X	X
Review subject glucose records	X	X	X	X	X	X	X	X	X	X	X	X
Assess study drug compliance				X	X	X	X	X	X	X	X	
Dietary counseling	X	X		X								
Hypoglycemia counseling	X	X		X	X	X	X	X	X	X	X	
Randomization				X								
Research Pharmacy Drug Dispensation				X			X				X	
AE Reporting		X	X	X	X	X	X	X	X	X	X	X

OUTCOME LABORATORIES													
Fasting Plasma Glucose		X			X	X	X	X	X		X	X	
Fasting Fingerstick Glucose			X				X						
Advanced lipid panel (lipoproteins, particle #/size)					X		X				X		
Adiponectin					X		X				X		
Exploratory biomarkers (cytokines)					X	X	X				X		
Fibrosis panel (Fibrotest)					X						X		
ProC3 (Nordic)					X		X				X		
CK-18					X						X		
Genotyping (SNPs of interest)					X								
IMAGING													
CAP and VCTE (Fibroscan)		X									X		
Liver IHTG content (1H-MRS)				X						X			
Liver fibrosis (MRE)				X						X			
T1 MR mapping				X						X			
INPATIENT METABOLIC TESTING													
Admit to CRC (research unit)					X						X		
Discharge from CRC					X						X		
Inpatient nursing staff assessment					X						X		
Study coordinator inpatient care					X						X		
Physician inpatient care					X						X		
Meal at CRC					X						X		
Overnight stay					X						X		
Insulin sensitivity study (clamp) with 6-6-2H glu infusion					X						X		
De novo lipogenesis (DNL) and gluconeogenesis					X						X		
Indirect calorimetry					X						X		
Urine collection for metabolic measurements					X						X		
* Not necessary if vailable within the past 12 months													
† CBC (complete blood count)		Red blood cell count, hemoglobin, hematocrit, WBC w/diff, platelet count.											
† CMP (comprehensive metabolic profile)		Glucose, electrolytes, albumin, total protein, calcium, bilirubin (BR), AST, ALT, alk phos (ALP), **INR.**											
† Lipids		Total cholesterol, HDL-C, LDL-C, non-HDL-C, triglycerides.											
# only if diabetes treatment modified since screening													

Table of contents

List of Tables

List of Figures

List of Abbreviations and Definitions of terms

^{1}H-MRS	Proton magnetic resonance spectroscopy
2D-MRE	Two-dimensional magnetic resonance elastography
AE	Adverse event
AHA	American Heart Association
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AST	Aspartate amino transferase
AUC	Area under the curve
BCS	Biopharmaceutics classification system
BDFDCS	Biopharmaceutics drug disposition classification system
BLM	Baseline measure
BMD	Bone mineral density
BMI	Body mass index
CA	Competent authority
CAP	Controlled attenuation parameter
CBC	Complete blood count
Cmax	Maximal plasma concentration
CPK	Creatine phosphokinase
CRC	Clinical research unit
CRF	Case report forms
CRO	Contract research organization
CTSI	Clinical Translational Science Institute
CVD	Cardiovascular disease
CYP	Cytochromes P450
D	Day
D2O	Deuterium labeled water
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DNL	De novo lipogenesis
DPP-IV	Dipeptidyl peptidase IV
DcSSc	Diffuse cutaneous systemic sclerosis
DSMB	Data safety and monitoring board
ECG	Electrocardiogram
ECM	Extra-cellular matrix
eCRF	Electronic case report forms
EDC	Electronic data capture
EGP	Endogenous glucose production
EMA	European Medicines Agency
ET	Early termination
FAS	Full analysis set

FDA	Food and Drug Administration
FPG	Fasting plasma glucose
γGT	Gamma glutamyl transpeptidase
GCP	Good Clinical Practice
GLP-1RA	Glucagon-like peptide-1 receptor agonists
^{1}H-MRS	Magnetic Resonance and Spectroscopy
h	Hour(s)
HbA1c	Glycosylated hemoglobin A1c
HBV	B virus hepatitis
HCV	C virus hepatitis
HIV	Human immunodeficiency virus
HDL-C	High-density lipoprotein cholesterol
HDPE	High-density polyethylene
HOMA	Homeostasis model assessment of insulin resistance
HSC	Hepatic stellate cells
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonization of Technical
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalized ratio
IHTG	Intrahepatic triglycerides
IRB	Institutional review board
IWRS	Interactive web response system
K/µL	103 cells/microliter
LDL-C	Low density lipoprotein cholesterol
L/kg	liter/kilogram
LXR	Liver X receptor
ml	Milliliters
ml/dL	Milliliters/deciliter
min	Minutes
µM	Micromolar
MCD	Methionine choline deficient
MCP	Monocyte chemoattractant protein
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
MH	Medical history
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic steatohepatitis
PCP	Primary care practitioner
PCR	Polymerase chain reaction
PCSA	Potentially clinically significant abnormalities

PDGF	Platelet-derived growth factor
PHI	Personal Health Information
PI	Principal investigator
PK	Pharmacokinetic(s)
PP	Per protocol
PPAR	Peroxisome proliferator-activated receptor
PTM	Placebo to match
QD	Once a day (Quaque Die)
QRS	QRS interval: duration in milliseconds of the QRS-complex
QT	QT interval: duration in milliseconds from the beginning of Q wave to the end of T wave
QTc	Corrected QT interval
RBC	Red blood cell
RH	Relative humidity
SAE	Serious adverse event
SAF	Steatosis activity fibrosis
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium-glucose co-transporter-2
SMA	α-Smooth muscle actin
SNP	Single nucleotide
SO	Safety officer
SUSAR	Suspected unexpected serious adverse reaction
TCA cycle	Tricarboxylic acid cycle enzyme activities
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TMF	Trial master file
TP	Prothrombin Time
T1 MRI	Magnetic resonance imaging
T2DM	Type 2 diabetes mellitus
UF	University of Florida
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of the normal range
UUO	Unilateral ureteral obstruction
V	Visit
VLDL	Very-low-density lipoprotein
VCTE-CAP	Vibration-controlled ttransient elastography and continuous attenuation parameter
Vz/F	Mean apparent volume of distribution
WBC	White blood cell

1 INTRODUCTION

This is a Phase II, randomized, double-blind, placebo-controlled, single-center, investigator initiated, 24-week treatment study of lanifibranor (IVA337) in adult subjects with Type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD).

This introductory section provides a rationale for the study, describes the underlying conditions of the patients to be included in the study, the scientific rationale for exploring lanifibranor in NAFLD, summarizes the lanifibranor preclinical and clinical data.

1.1 Study Rationale

Nonalcoholic fatty liver disease (NAFLD) develops in ~70% of patients with type 2 diabetes mellitus (T2DM) (7,8) and about 40% develop the more severe form of the disease with hepatocyte necrosis (ballooning) and liver inflammation (steatohepatitis or NASH). This is often in diabetes associated with fibrosis progression and a higher risk of developing cirrhosis. Of note, diabetes is the single most important clinical risk factor for NASH progression. This is particularly true in the setting of obesity, where insulin-resistant (dysfunctional) adipose tissue promotes hepatic steatosis and hepatocyte injury from "lipotoxicity" (12). Patients with T2DM and NASH are also at increased risk of micro- and macrovascular complications (7-13). Taken together, it is likely that clinicians managing patients with T2DM will give preeminence to treatments that not only control hyperglycemia, but also treat liver disease (NASH). Unfortunately, treatment options for NAFLD/NASH remain limited although many drugs are in development, as reviewed recently elsewhere (13,14). Successful treatments for NASH will likely need to reverse liver insulin resistance (7,8 - see below). Lanifibranor (IVA337), a pan-PPAR α, δ and γ, may improve or normalize hepatic insulin sensitivity, intrahepatic triglyceride (IHTG) accumulation, excessive de novo lipogenesis (DNL) and VLDL oversecretion (i.e., atherogenic dyslipidemia) in humans but this remains to be tested. This may be due to either a direct effect on intracellular glucose or lipid metabolism effects in hepatocytes, kupfer and stellate cells. As obesity reaches epidemic proportions, nonalcoholic fatty liver disease (NAFLD) is becoming a frequent cause of patient referral to gastroenterologists. There is a close link between dysfunctional adipose tissue in NAFLD and common conditions such as metabolic syndrome, T2DM, and cardiovascular disease. The following focuses on the pathophysiology of interactions between adipose tissue and target organs in obesity and the resulting clinical implications for the management of nonalcoholic steatohepatitis. The release of fatty acids from dysfunctional and insulin-resistant adipocytes results in lipotoxicity, caused by the accumulation of triglyceride-derived toxic metabolites in ectopic tissues (liver, muscle, pancreatic beta cells) and subsequent activation of inflammatory pathways, cellular dysfunction, and lipoapoptosis. The cross talk between dysfunctional adipocytes and the liver involves multiple cell populations, including macrophages and other immune cells that in concert promote the development of lipotoxic liver disease, a term that more accurately describes the pathophysiology of nonalcoholic steatohepatitis. At the clinical level, adipose tissue insulin resistance contributes to type 2 diabetes mellitus and cardiovascular disease. Treatments that rescue the liver from lipotoxicity by restoring adipose tissue insulin sensitivity (e.g., significant weight loss, exercise, thiazolidinediones) or preventing activation of inflammatory pathways and oxidative stress (ie, vitamin E, thiazolidinediones) hold promise in the treatment of NAFLD, although their long-term safety and efficacy remain to be established. Better understanding of pathways that link dysregulated adipose tissue, metabolic dysfunction, and liver lipotoxicity will result in improvements in the clinical management of these challenging patients (7), or indirectly, through PPAR δ and/or γ effects on peripheral adipose tissue or muscle insulin signaling pathways.

This study will test the hypothesis that treatment with lanifibranor will significantly decrease liver steatosis (primary endpoint) in patients with T2DM and NAFLD. It will also aim to understand the mechanism(s) of action of IVA337 associated with a reduction in liver fat. Specifically, we will examine the effect of IVA337 on hepatic pathways linked to the development of hepatic steatosis,

insulin resistance and atherogenic dyslipidemia (hepatic insulin sensitivity, endogenous [largely hepatic] glucose production and gluconeogenesis, DNL and VLDL secretion) with the use of gold-standard stable isotope metabolic techniques. This will establish a robust rationale for the use of IVA337 in NAFLD and will complement the results of the Phase IIb RCT (NATIVE trial) on its effect on liver histology in NASH, where there was a significant improvement in the primary endpoint (SAF-A score and no worsening of fibrosis in 48% with 800 mg/day (p=0.07) and in 55% with 1,200 mg/day of lanifbranor (p=0.007) vs. 33% with placebo. Secondary endpoints significant with both doses included resolution of NASH without worsening of fibrosis were and in the composite endpoint of resolution of NASH and improvement of fibrosis.

1.2 Previous Studies in Patients NAFLD/NASH and T2DM and Interest of Assessing the Metabolic Effects of the Pan-PPAR IVA337

There is limited data on pharmacological treatments for this population (13,14). Treatment of NASH with DPP-IV inhibitors have met mixed results in NAFLD (8,13), while the potential of GLP-1RAs is more promising. For instance, during clinical development it was observed that liraglutide lowered elevated plasma aminotransferases in patients with T2DM (15). However, it was not until recently that GLP-1RAs were reported to reverse metabolic (16) and histological (17) defects in NASH. In the study by Armstrong et al (17), resolution of NASH occurred in 39% of patients treated with liraglutide versus 9% treated with placebo (p=0.019; treatment difference ~30%). Of note, liraglutide improved some but not all histological features. There was a decrease in steatosis (83% vs. 45%; p=0.009; ~35% reduction in mean steatosis cores from baseline) and hepatocyte ballooning (61% vs. 32%; p=0.05). Insulin sensitivity at the level of the liver and adipose tissue improved in a subset of patients undergoing in-depth metabolic studies at 3 months (16). However, the study was small and only one-third of patients had T2DM. Moreover, recently Tang et al (18) recently reported no effect of liraglutide on liver fat in patients with T2DM and NAFLD. Therefore, the role of GLP-1RAs in patients with T2DM and NAFLD remains to be fully established.

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that function as transcription factors regulating the expression of genes essential for cellular differentiation, and development, as well as in key pathways of carbohydrate, lipid and protein (1). PPARα is highly expressed in the liver and its activation by fibrates modulates fatty acid transport and β-oxidation, inflammatory pathways, and improves the plasma lipoprotein profile observed in insulin-resistant states, but not glucose metabolism (19). Moreover, fibrates do not reduce hepatic triglyceride concentration in NAFLD (20). PPARδ agonists also promote fatty acid transport and β-oxidation, increase plasma HDL-C concentration, and exert anti-inflammatory actions in macrophages and Kupffer cells (19), but in addition may improve glucose metabolism by enhancing insulin hepatic insulin sensitivity (21,22). These features are attractive for the treatment of NASH. However, recently elafibranor, a PPARα/δ agonist, failed to meet the primary endpoint of resolution of NASH in the GOLDEN trial but reported histological benefit in patients with a higher NAS score (≥ 4) (23). Thiazolinediones (TZDs) are ligands for the transcription factor PPAR-γ that plays a key role in the regulation of glucose and lipid metabolism, as well as in inflammation. Belfort et al were the first to report in a RCT that a PPAR-γ ligand (pioglitazone) could improve liver histology in patients with NASH and also having prediabetes or T2DM (1). There was also a suggestion that fibrosis could be reversed in NASH, as pioglitazone-treated patients had a significant reduction in liver fibrosis compared to baseline, although this fell short of reaching statistical significance when compared to placebo (p=0.08). This was later also demonstrated in non-diabetic patients (7,14). Recently, Cusi et al. reported in a 36-month study in 101 patients with prediabetes or T2DM and NASH that pioglitazone led to sustained histological and metabolic benefit (2). Of note, there was also a modest but statistically significant difference in the mean scores for fibrosis when compared to placebo. The effect of pioglitazone in patients with advanced fibrosis (F2-3) has been suggested from a recent meta-analysis combining all recent RCTs (24).

Animal models of NASH offer powerful evidence that the pan-PPAR IVA337 can improve insulin action, increase adiponectin, improve liver histology and have anti-inflammatory and anti- fibrotic properties (data on file Inventiva and 25). It is also likely that IVA337 may improve mitochondrial defects that are at the core of the paradigm linking excess substrate supply (fatty acids), insulin resistance, hepatocyte "lipotoxicity" and steatohepatitis, as recently reviewed (26,27). Recent studies from our laboratory (28,29), and others (30,31), support the role of mitochondrial dysfunction in NASH. Recent human studies indicate inadequate mitochondrial adaptation despite increased TCA cycle activity in obese patients with NASH (32) and we have developed the methodology to study mitochondrial function in clinical trials (33).

In humans, the mechanism of action of IVA337 remains to be further assessed. In the 4-week PK/PD Phase IIa study in patients with T2DM, IVA337 had a mild glucose-lowering effect. It is unclear if the limited glucose-lowering effect was due to a lack of efficacy per se or was related to the short-term 4- week exposure. However, treatment improved lipids and markedly increased plasma adiponectin concentration. As mentioned above, liver histology improved in the Phase IIb NATIVE RCT, being important at the same time to establish the mechanism of action and metabolic effects of IVA337 on hepatic, muscle and/or adipose tissue insulin sensitivity in patients in NASH, as reported for liraglutide (16,17) or pioglitazone (1,2) in insulin-resistant and/or T2DM patients. An attractive feature of IVA337 is its ability to impact through its PPAR α/δ profile lipid pathways and likely reduce increased rates of DNL and hepatic VLDL secretion that drive the atherogenic dyslipidemia and CVD in NAFLD. Pioglitazone, possibly by its PPAR α properties, has been reported to reduce DNL in humans (34) and lower plasma triglyceride concentration in association with an improvement in mitochondrial defects that drive hepatic steatohepatitis (7,31). Treatment with IVA337 would be well suited to address these defects but requires additional investigations in T2DM.

In summary, given IVA337's apparent clinical efficacy and overall safety (i.e., a PPAR that is apparently weight neutral and does not cause fluid retention), it may hold a significant advantage over traditional PPARγ agonists and other drugs in development for NASH. We hypothesize that IVA337 will have a profound impact on liver metabolism, reducing hepatic triglyceride content and improving hepatic insulin sensitivity in patients with T2DM and NAFLD/NASH. Therapies that can reduce hepatic steatosis/TG synthesis/DNL and VLDL oversecretion will likely become first-line therapy for patients with T2DM and NASH. This work will open a new horizon for IVA337 as an insulin-sensitizer and position it as a key player in the management of these patients.

1.3 Investigational Product

Lanifibranor (IVA337), 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:	β form crystal

The Investigational Medicinal Product is a white to off-white bi-convex tablet, weighing approximately 927 mg and showing a breakline to facilitate the administration to patients. The film-coated tablet contains 400 mg of the active ingredient lanifibranor (IVA337) for an immediate release formulation.

Film-coated tablets with a core containing 900 mg of a physical mixture of lactose monohydrate, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate serve as placebo.

The Investigational Medicinal Products used in this clinical Phase II trial will be packaged in

containers of High Density Polyethylene (HDPE) with proper HDPE closures fitted with a silica cartridge.

Based on the results of the ongoing stability studies, a shelf life of 2 years (storage at 25°C or below) is proposed for the Investigational Medicinal Product provided it is stored in the original package, the HDPE bottles.

Furthermore, the stability data at 40°C/75%RH demonstrate that temperature excursions (e.g. during shipment, storage) will not significantly affect the stability of lanifibranor 400 mg film-coated tablets.

To avoid the potential moisture ingress, which may happen during the use of the monthly pack, a twist-off cap integrated with a 2 g of silica gel has been selected for the closure. The data of the "in use test" 35 days at 25°C/60%RH open bottles have confirmed the stability of the Investigational Medicinal Product during its proposed clinical use.

A new formulation has been developed to reduce the size of the lanifibranor tablet and improve compliance to the treatment. The two formulations are be considered as similar as demonstrated by a bio-equivalence clinical study (337HVPK18006 trial). All characteristics of the investigational product remain the same except that the new formulated lanifibranor tablet has a weigh of approximately 721 mg and a shelf life is of 3 years based on the results of the ongoing stability studies.

Matching film-coated tablets with a core containing 700 mg of a physical mixture of lactose monohydrate, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate have also been developed to serve as placebo.

Upon protocol approval, any new subject enrolled will be administered with the new formulation. For subjects under treatment, the switch to the new formulation will be made at the next study visit post protocol approval with respect to the initial assignment to treatment arm.

1.4 Summary of Lanifibranor Preclinical and Clinical Data

1.4.1 Pharmacology

NAFLD/NASH is a multifactorial and multi-step disease. A first component of this pathology includes the metabolic syndrome related to insulin resistance, triglyceride accumulation, obesity etc. A second component is the fibrosis. In our pre-clinical studies, we demonstrated the beneficial effect of IVA337 in several components of the metabolic syndrome as well as in fibrosis.

IVA337, in previous experiments, was shown to exert an anti-diabetic and antihyperlipidemic activity in db/db mice, ZDF rats, diet-induced obese mice and the WOKW rat model of metabolic syndrome. Furthermore, it increased serum apoA1 level in human apoA1 transgenic mice. In functional cellular tests, IVA337 increased fatty acid β-oxidation, stimulated cholesterol efflux, induced the expression of aP2 and adiponectin genes as well as ABCA1, ABCG1 and LXRα genes, while it reduced MCP-1 secretion. All these effects are signature of the activation of the 3 PPAR receptor isoforms.

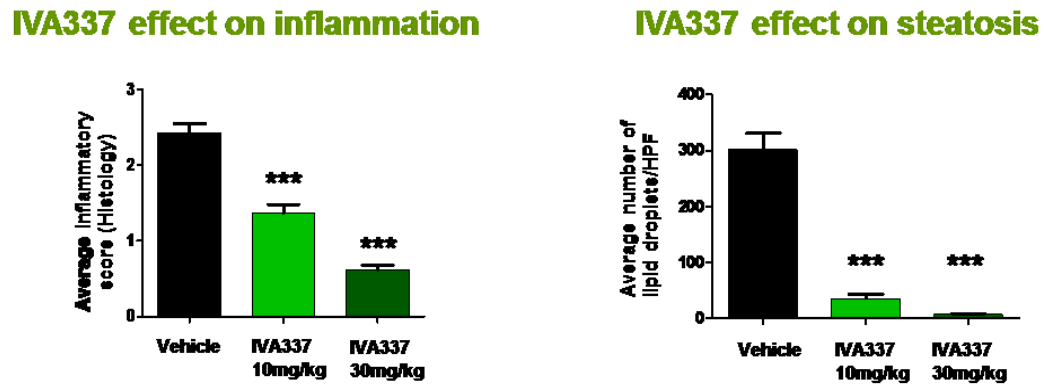
Recently, it was demonstrated in vivo that IVA337 displays an antifibrotic activity in bleomycin-induced lung fibrosis, in bleomycin-induced skin fibrosis (in preventive and curative mode), in a model of unilateral ureteral obstruction (UUO)-induced kidney fibrosis and in CCL4-induced fibrosis in the liver. In the liver, IVA337 is active in both preventive as well as curative mode, thus providing evidence for an anti-fibrotic effect in established fibrotic disease. In the liver it was demonstrated that IVA337 at 15 and 30 mg/kg was able to inhibit in a dose dependent manner the collagen deposition within the liver (-42% and -73.16% respectively). IVA337 was also able to decrease the serum triglycerides and ALT.

HSC are the cells responsible for the secretion the Extra-Cellular Matrix (ECM) and especially the

collagen when activated (myofibroblast transdifferenciation of HSC). The main cellular process underwent by the HSC in a fibrogenenic environment is proliferation and activation. The proliferation assay is based on PDGF and the activation is based on stiffness (stiffness of the plated plastic). PDGF is secreted by a variety of cell types and plays a central role in fibrogenesis. It induces HSC proliferation and migration, thus contributing to the increase of the number of matrix-secreting cells. During fibrosis, the growing deposition of ECM increases the stiffness of the liver and participates to myofibroblast transdifferentiation of HSC. IVA337 was able to fully inhibit the proliferation induced by PDGF and was able to prevent the overexpression of α-SMA and the hallmark of myofibroblast, induced by stiffness. These findings strongly support the anti-fibrotic action of IVA337 in the target cells.

Activity of IVA337 on liver steatosis and inflammation, two main components of NASH, was evaluated in a 3-week model of MCD diet in C57bl/6 mice (report in preparation). It was shown that IVA337 prevented steatosis in a dose-dependent manner at the doses of 10 and 30 mg/kg (-88.38% and -97.89% respectively compared to vehicle, see Figure 2). IVA337 also prevented inflammation at the doses of 10 and 30 mg/kg (-44.03% and -74.49% respectively compared to vehicle). IVA337 also prevented the increase in ALT transaminase induced by MCD diet (-49.35% and 67.26% at 10 and 30 mg/kg respectively), demonstrating hepatoprotective effect.

Figure 2. IVA337 Reduces Inflammation and Steatosis in a 3 Weeks MCD Model



1.4.2 Pharmacokinetics

IVA337 can be considered as a class II compound as regard to the Biopharmaceutics Classification System (BCS) Guidance and Biopharmaceutics Drug Disposition Classification System (BDDCS): high permeability and metabolism, and low solubility. It was evidenced in all tested pecies that IVA337 absorption is dependent on the drug substance form and formulation, leading to a bioavailability in animals from 15% up to > 80%. An enterohepatic recycling was evidenced, and a food effect was observed in human in the presence of high fat breakfast.

After oral administration in humans, maximum plasma levels (C_{max}) of IVA337 were reached at about 1.0-3.5 hours, and terminal plasma elimination half-life was around 10-15 h. Both AUC and C_{max} increased in a linear but slightly less than dose-proportional manner. Steady-state IVA337 concentrations were generally achieved by Day 3 after daily dose administration, with no significant accumulation.

The mean apparent volume of distribution Vz/F ranged from 318 to 607 L in healthy subjects. IVA337 was extensively distributed in monkeys (~10 L/kg). IVA337 binds very highly to plasma proteins in all tested species (~99.9%) and no affinity to blood cells was observed. By autoradiography in rat, IVA337 was shown to be mainly distributed in the excretory organs (liver,

kidneys, lungs, gastrointestinal tract) and in placenta in pregnant rats with no affinity for the melanin tissues and with very limited central nervous system distribution.

IVA337-related radioactivity elimination in human was mainly fecal (> 85%) and the urinary excretion was minor (< 7%) with a very low renal clearance. The excretion was essentially complete after 3 days.

AUC indicated that approximately 23% of the radioactivity in human plasma were related to IVA337, while 77% were related to its metabolites.

Among metabolites identified in plasma, feces and urine, the main IVA337 metabolites observed in human were the acylglucuronide (IV1197736, with similar exposure to that of the parent compound), a monohydroxylated (IV1537661) and the benzothiazole ring opened IVA337 derivative (IV1197347). All other metabolites were reported to represent less than 5% of the administered dose (14C-ADME study in human). The completion of the quantitative comparison of the animal versus human plasma exposure to these three metabolites is ongoing.

In vitro data on drug-drug interaction of IVA337 and its three main human metabolites were completed. The data interpretation was done following EMA and FDA guidelines on the investigation of drug interactions, considering the therapeutic dose of 1200 mg (C_{max} ~20 µM) and estimated parameters (Ka, Fa) from population PK modelling.

As victim, the pharmacokinetic of IVA337 or its main human metabolites was observed in vitro to be possibly sensitive to the pathways CYP2C8, CYP2C19, CYP3A4, UGT1A1, UGT1A3, UGT2B7, MRP2, MRP3, OATP1B1 and OATP1B3. As several isoforms of each enzyme are involved (CYP and UGT), a risk of clinical interaction via these pathways is reduced. Nevertheless, the contribution of CYP isoforms to the formation of the main Phase I metabolites is still to be exemplified. As regards to transporters, clinical data would be required to assess the possible interaction of comedications on the IVA337 via these pathways.

As perpetrator, in vitro studies evidenced that IVA337 or its main human metabolites may have an impact on the pharmacokinetics of drugs which are sensitive to the pathways CYP2B6, CYP2C8, UGT1A1, UGT1A4, UGT2B7, BCRP, MRP2, MRP3, OATP1B1, OATP1B3, and at the intestine level MDR1, and at the kidney level OAT1 and OAT3. In silico modelling will be conducted for a deeper analysis on the CYP and OAT interactions. As regards to MDR1, BCRP, OATP and MRP transporters, clinical studies would be conducted to assess the possible interaction of IVA337 on comedications via these pathways. A first study was performed with simvastatin, substrate of several pathways (MDR1, BCRP, OATP1B1 but also CYP3A4 and CYP2C8), which seemed not to evidence a significant drug-drug interaction (< 2-fold) although the increase of simvastatin C_{max} may possibly be due to MDR1/BCRP intestinal inhibition.

A limited risk of CYP induction could be expected in vivo. No induction CYP1A2 or CYP2B6 in any of the human hepatocyte donors tested when incubated by IVA337 (N=7) or its metabolites (N=3). A slight mRNA CYP3A4 induction was observed (2.3-12 fold, equating to 0.5-28 % of the response observed with rifampicin) at 12.5 µM while a mRNA repression was observed at higher concentrations. CYP3A4 enzyme activities (studied in four donors with IVA337) was shown to be slightly induced in two donors after incubation with IVA337 but only with high concentration (> 40 µM).

No significant drug-drug interactions were observed with simvastatin and IVA337 (< 2-fold), and no PK/genotype (CYP450 isoenzymes and UGTs isoform) relationship has been identified. There was a 22% increase in C_{max} and 39% increase in AUC of IVA337 in elderly subjects as compared to young subjects.

1.4.3 Toxicology

IVA337 has a very low acute toxicity (maximal non-lethal dose of 2000 mg/kg in rodents) and is

not irritating to the skin.

IVA337 is devoid of genotoxic potential in the full international conference on harmonization (ICH) battery of genotoxicity assays. The three major human metabolites, IV1197736, IV1197347 and IV1537661, were also found devoid of genotoxic potential in a bacterial reverse mutation test and a mammalian cell assay.

IVA337 is devoid of deleterious effects on vital functions such as cardiovascular, central and autonomic nervous system and respiratory system. In a 9-week head-to-head comparative study in rats aimed at evaluating side effects of PPAR agonists such as plasma volume expansion and secondary cardiac hypertrophy, or skeletal muscle toxicity, daily doses of IVA337 up to 1000 mg/kg compared favorably with other PPAR agonists rosiglitazone, muraglitazar and tesaglitazar. These observations were substantiated in repeated dose toxicity studies with IVA337 in rats and monkeys.

No potential risks have been identified from pivotal toxicology studies with IVA337 in rat and in monkey and segment II reproductive toxicity studies in rats and rabbits. All treatment-related findings (i.e. liver, bone marrow, adipose tissue) were reversible.

The safety margins over expected human exposure in general toxicology studies were at least 20-fold in rats and 3-fold in monkeys (Table 2). The safety margins over expected human exposure established in segment II reproductive toxicity studies were 9-fold in rats and 2-fold in rabbits (Table 3). A preliminary 2-week pharmacokinetic and toxicity study in the mouse, where plasma exposures were markedly higher than those achieved in volunteers given the highest tested dose of 1500 mg/day for two weeks (approximately 40-fold) and higher than those achieved in the chronic rat study, has evidenced signs of toxicity for the kidney, the heart and the skeletal muscles, in particular myositis of skeletal muscles, minimal to moderate myocarditis and tubulo-interstitial nephritis. These organs are known targets for toxicity of PPAR agonists. However, a recently conducted 13-week study in mice established an adequate 5-fold safety margin over expected human exposure at a NOAEL (no observed adverse effects levels) of 25 mg/kg/day.

Table 2. Interspecies Comparison of Human and Animal Plasma Exposure to IVA337 in General Toxicity Studies

Human Plasma AUC at Estimated Active Dose (µg.h/mL)	Species	NOAEL Male-Female (mg/kg/d)	AUC at NOAEL Male-Female (µg.h/mL)	Safety Margin
50	Mouse*	25	225 - 278	~5
	Rat**	2000 - 1000	798 - 1144	16 - 23
	Monkey##	1000	110 - 82	1.6 - 2.2

*: from 13-week toxicology study in CD-1 mice

**: from 13-week toxicology study in Wistar rats

##: from 26-week toxicology study in Cynomolgus monkeys

Table 3. Interspecies Comparison of Human and Animal Plasma Exposure to IVA337 in Segment II Reproductive Toxicity Studies

Species/Strain	NOAEL (mg/kg/d)	Plasma Exposure (AUC0-24 as µg.h/mL)	
		Gender	lanifibranor
Han Wistar Rat	100	Female	437 (8.7)[1]
New Zealand White	Rabbit		

3	Female	105 (2.1)

[1] values in brackets show exposure margin factor to clinical exposure

1.4.4 Previous IVA337 Clinical Data

IVA337 has previously been in clinical development up to Phase II for the treatment of type 2 diabetes. The development for diabetes was discontinued for strategic reasons.

Three clinical studies have been conducted in healthy subjects, one study in patients with type 2 diabetes, and one Phase II study is ongoing in the treatment of diffuse cutaneous systemic sclerosis. The objectives of study S337.1.001 were to assess pharmacokinetics, pharmacodynamics, safety and tolerability of IVA337 after single increasing doses and after multiple increasing doses. The objectives of study S337.1.002 were to study the effect of IVA337 on the pharmacokinetics of simvastatin and simvastatin acid and to evaluate the pharmacokinetics of the two-crystalline anhydrous solid alpha and beta forms of IVA337. The objectives of study S337.1.005 were to assess the relative bioavailability of IVA337 oral suspension and capsules (cross-over design), and to assess, in vivo in human, the completeness of excretion, routes and rates of elimination of radioactivity, the metabolic pathways, and identity of IVA337 metabolites after single administration of 14C-IVA337. The objectives of study S337.2.001 were to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of IVA337 in doses of 400 to 1200 mg daily over a 4-week period. The study IVA_01_337_HSSC_15_001 is a randomized, double- blind, placebo-controlled, multicenter proof-of-concept trial of IVA337 in the treatment of diffuse cutaneous systemic sclerosis (DcSSc).

The study IVA_01_337_HNAS_16_002 is a randomized, double-blind, placebo- controlled, multicenter, dose-range, proof-of-concept, 24-week treatment study of IVA337 in adult subjects with nonalcoholic steatohepatitis (NASH).

In clinical trials performed in healthy volunteers and patients with type 2 diabetes, IVA337 was safe and well tolerated. Treatments included single doses of 25 mg to 1000 mg, multiple doses of 150 mg to 1500 mg once daily for 14 consecutive days, and once daily doses of 400, 800, and 1400 mg for 4 weeks. The reported treatment emergent adverse events considered to have a causal relationship to the study drug included dizziness, postural dizziness, headache, hot flush, lethargy, somnolence, constipation, trends towards decreases in red blood cell count, hemoglobin and hematocrit in healthy volunteers, and hypochromic anemia, constipation, urinary tract infection and headache in patients with type 2 diabetes. There were no clinically relevant time or dose-related changes on cardiac and muscle markers, liver enzymes or markers of renal function. The 12-lead electrocardiogram (ECG) did not show clinically significant changes.

1.5 Rationale of the Study Design

1.5.1 General Considerations

This study is a Phase II randomized, double-blind, placebo-controlled, single-center, investigator initiated, 24-week treatment study of lanifibranor in adult subjects with T2DM and NAFLD.

1.5.2 Rationale for the Choice of Dose and Duration of Repeated Administration

The evaluated treatment will be as tablets of lanifibranor 400 mg, one dose of lanifibranor, 800 mg once a day (QD) versus placebo, i.e. two tablets (lanifibranor or indistinguishable placebo) per os, once daily, for 24 weeks. To improve bioavailability, drug intake is combined with food.

The dose has been selected based on the available biomarker (adiponectin, HDL cholesterol, triglycerides) results in diabetes type 2 patients (Phase IIa study): 800 mg per day: lowest and statistically significant active dose on the markers of the three PPAR α, δ and γ activity and being well tolerated

Pharmacodynamic biomarkers of PPARs activation in diabetic patients (Phase IIa study) are shown in Figure 3.

Clinical, biological and ECG safety in healthy volunteers and diabetic patients has been shown to be good up to the top dose used in this trial or at doses that are higher. There is no toxicology target organ of major concern in the clinic.

Placebo is chosen as the comparator, as there is no licensed treatment for NAFLD/NASH.

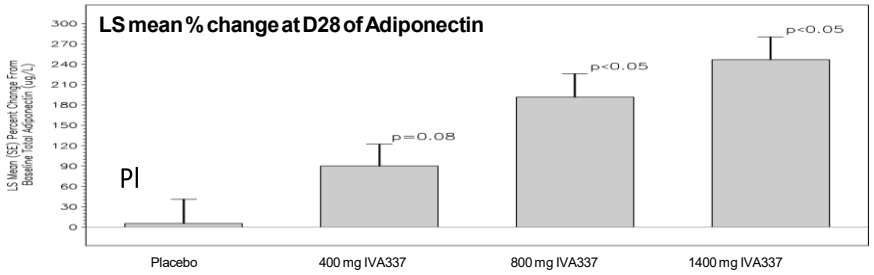
Treatment duration has been set to 6 months. This is a Phase II study and the aim to assess safety efficacy and mechanism of action. Improvement in ALT, AST, γGT as well as insulin resistance can be observed within a couple of months of treatment, as has been observed in several trials seen with other PPARs agonists (1, 23), suggesting that treatment efficacy can be observed early in the course of treatment. Significant effect on hepatic steatosis and necroinflammation has been reported before at 6 months with a PPARγ agonist (1).

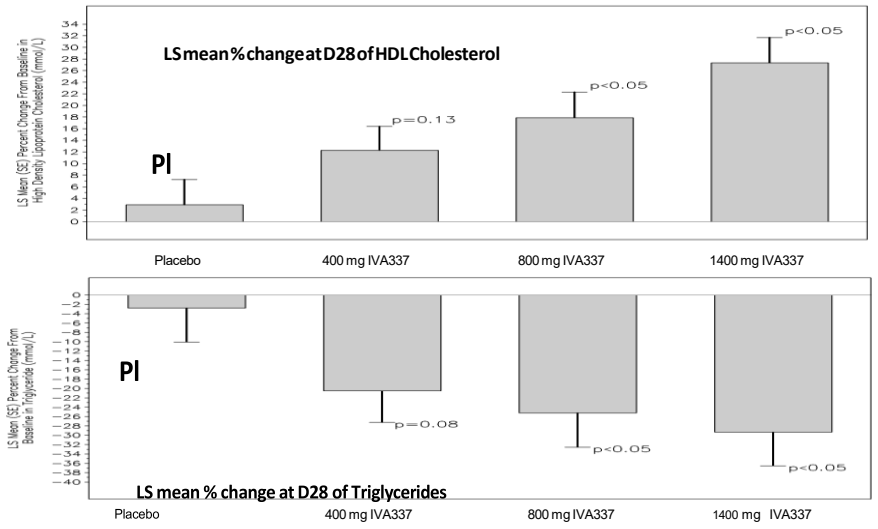
The study imposes 10 visits including the screen and follow-up visits and, apart periodic blood sampling, there are no other invasive procedures. There is a very limited number of prohibited medications that should not interfere with standard medical care of the patients.

For obvious reasons, fibrates, as they are PPARα ligands, are not allowed, but dyslipidemias can be treated with statins, which are allowed.

Half of the patients is on verum treatment and can expect an improvement of their NAFLD and metabolic syndrome based on the results of previous clinical studies with PPARα, γ and α/δ agonists. The dose chosen for the trial demonstrated significant improvement in biomarkers of PPAR α, γ and probably δ in diabetic patients.

Figure 3. Phase IIa Biomarkers of IVA337 PPAR Activation in Diabetic Patients





2 Investigators and Study Administrative Structure

2.1 Investigators and Other Participants

The study will be performed in at the University of Florida (Endocrinology, Diabetes and Metabolism Division; and the Clinical Translational Research Institute), Gainesville, Florida.

Principal Investigator: Pr. Kenneth Cusi, M.D., F.A.C.P., F.A.C.E.

Professor of Medicine

Chief, Division of Endocrinology, Diabetes and Metabolism

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Direct phone: 352-294-5723

Division phone: 352-273-8662

Co-investigators:

Diana Barb, M.D.

Romina Lomonaco, M.D.

Eddison Godinez Leiva, MD.

Troy Donahoo, M.D.

Julio Leey, MD

Other participants:

Srilaxmi Kalavalapalli, Medical Scientist (Laboratory Director)

Robert Campbell, Study Coordinator

2.2 Role of Inventiva SA and Representatives

Inventiva SA will provide the treatment units and regulatory support to assist the Principal Investigator in the filling of an investigator-initiated IND.

Inventiva SA will compensate the investigator and his institution for all study related costs.

Inventiva S.A

50 rue de DIJON, 21121 Daix, France
Phone: +33 (0) 380 447 680
Chief Medical Officer (CMO): Dr Michael Cooreman, MD
Phone: +33 (0) 380 447 500
Email: michael.cooreman@inventivapharma.com.

2.3 Pharmacovigilance and Safety

The Principal Investigator will ensure the safety of the study following GCPs and FDA regulations.

2.4 Other Relevant Institutions

Cusi Lab
1600 SW Archer Road Room R4-135
Gainesville, FL 32610

Shands Path Lab
4800 SW 35th Drive
Gainesville, FL 32608

Product Manufacturing:

DELPHARM, 10 rue Charbonneaux, 51100 Reims France
Phone: +33 (0) 3 80 48 30 30

Clinical Packaging:

Amatsi group, 17 Rue des Vautes, 34980 Saint-Gély-du-Fesc, France
Phone: +33 (0) 4 99 58 38 60

3 Ethical and Legal Considerations

The principal investigator will obtain the approval of the study from the Competent Authority (CA) and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The IRB and CA receive annual safety and interim reports and are informed about study stop/end in agreement with local requirements.

3.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The Principal Investigator will submit this protocol to the University of Florida IRB, and will forward to the Inventiva SA a copy of the written and dated approval (and annual reapproval) in order to allow delivery of the treatment units.

The study (study number, Protocol title and version number), the documents reviewed (protocol, Informed Consent Form, Investigator's brochure, etc.) and the date of the review should be clearly stated on the written IRB approval. All correspondence with the IRB should be retained in the Investigator File.

Investigational Medicinal Product will not be released at the study site and the trial will not start until a copy of written and dated approval favorable opinion has been received by the Principal Investigator and by Inventiva S.A.

3.2 Protocol Amendments

Inventiva S.A. will be informed of any change done by the Principal Investigator

The change, presented as an amendment in written form to the protocol, will be signed by the Investigator and submitted to the IRB and whenever applicable to the CA for their approval.

The amendment cannot be acted upon prior to the outcome of this decision.

Amendment regarding minor modifications (administrative modifications) will be submitted to the IRB/IEC for information purposes only and whenever applicable to CA.

The only circumstance in which an amendment may be initiated prior to IRB and CA approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB and Inventiva S.A. in writing immediately after the implementation. All updates to the Investigator's Brochure, Protocol or any amendment-impacted documents will be sent to the IRB/IEC and CA whenever applicable.

If requested, a progress report could be sent to the IRB annually and a summary of the trial's outcome could also be provided at the end of the clinical trial.

3.3 Ethical Conduct of the Study

This protocol complies with the principles laid down by the 64th World Medical Assembly (Fortaleza, October 2013) and all applicable amendments laid down by the World Medical Assemblies, the guidelines of Good Clinical Practice CPMP/ICH/135/95 and applicable regulations, and any other relevant local requirement and laws.

3.4 Good Clinical Practice Responsibilities

The responsibilities of the Principal Investigator will be as defined in the ICH GCP guidelines and applicable regulatory requirements. The Principal Investigator is responsible for adhering to the responsibilities of investigators, for dispensing the IMP in accordance with the final protocol or an approved amendment, and for its secure storage and safe handling throughout the study.

3.5 Reporting of Safety Issues Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed by an applicable CA, or if the Principal Investigator is aware of any information which might influence the evaluation of the benefits and risks of the IMP, Inventiva S.A. should be informed immediately.

In addition, the Principal Investigator will inform Inventiva S.A. immediately of any urgency safety measures taken by the Principal Investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the Principal Investigator becomes aware of.

3.6 Insurance

In case of a damage or injury occurring to a patient in association with the IMP or the participation in the study, the University of Florida has subscribed for itself and the Principal Investigator and

the medical team working in the clinical trial to an insurance policy covering, in its terms and provisions, their legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards »

3.7 Patient Information and Consent

The Principal Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the Ethics Committee (IRB/IEC).

Prior to a patient's participation in the clinical trial, the Informed Consent Form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

The Informed Consent Form used by the Investigator for obtaining the patient's informed consent must be reviewed by Inventiva S.A. prior to submission to the appropriate IRB for approval/favorable opinion.

Signed consent forms must remain in the Investigator file and must be available for verification by study monitors or authorized regulatory representatives at any time.

The patient should receive a copy of the signed and dated written informed consent form. Any amendments to the written information will be provided to the patients.

3.8 Premature Termination

Both the Principal Investigator and Inventiva SA reserve the right to terminate the study at any time. Should this become necessary, the procedures will be agreed after consultation between the two parties. In terminating the study, the Principal Investigator will ensure that adequate consideration is given to the protection of the best interests of the patients.

3.9 Definition of End of the Trial

End of trial is defined as the last visit (Visit 10, planned at the end of the 28-day off-drug follow-up period), of the last patient as defined in the protocol.

4 Study Objectives and Investigational Plan

4.1 Aim

The primary aim is to establish the safety, efficacy and mechanism of action of lanifibranor in patients with NAFLD and T2DM.

Specifically, to determine if lanifibranor decreases IHTG (primary endpoint), improves hepatic insulin sensitivity, endogenous (hepatic) glucose production, gluconeogenesis and de novo lipogenesis (DNL). This will be achieved by using a combination of intravenously infused stable isotopes and with the infusion of a low- and high-dose insulin infusion during a euglycemic hyperinsulinemic clamp (to quantify insulin action) with indirect calorimetry (to measure substrate oxidation). In addition, exploratory analysis with surrogate plasma biomarkers and imaging on changes on liver fibrosis with treatment will be performed.

4.2 Study Design

The study is a two-arm (placebo, lanifibranor 800 mg/day), randomized (1:1), double-blind, placebo-controlled, 24-week treatment study. There is in addition a non-obese subject control group for the metabolic and imaging procedures.

The study will require 32 ± 4 weeks (4-6 weeks for run-in, 24 weeks of treatment and 4 weeks post-study follow-up), with an estimated recruitment period of 6 to 9 months.

Patients to be randomized: 34 allowing for a 10% drop-out rate.

The overall study design is shown in Figure 1.

Study Duration and Procedures

For each patient, the research study will be divided as follows:

- Run-in period: Screening visit **V1**, DM medication titration **V2**, Baseline studies **V3** and Randomization **V4.**
- Interim **V5** (4 weeks after V4), Interim **V6** (8 weeks after V4), Interim **V7** (12 weeks after V4), Interim V8 (16 weeks after V4), Interim V9 (20 weeks after V4).
- Repeat baseline studies **V10** (23 weeks after V4) and **V11** (24 weeks after V4).
- Off-drug Follow-up visit **V12** (28 weeks after V4).

4.2.1 Screening Phase

We plan to recruit patients with uncontrolled T2DM and a diagnosis of "fatty liver" per history (elevated AST/ALT and/or liver fat on liver ultrasound or ^{1}H-MRS and/or other appropriate imaging technique – see below). A Fibroscan study available in the research unit will be performed at the initial screen visit.

CAP test (Fibroscan: ultrasound-based elastography available in the PI's outpatient clinic and also research unit) will be performed at the initial screening visit to identify those patients with a fatty liver.

The goal of the screening is therefore to check inclusion and exclusion criteria and adjust T2DM treatment as described below.

Participants may be treated by diet only, or be on a stable dose of metformin and/or a sulfonylurea and/or a DPP-IV inhibitor for ≥ 2 months prior to enrollment. If the HbA1c is ≤8.0% on any of these diabetes medications, the dose of these medications will be kept stable throughout the study and baseline studies performed as outlined below. If the HbA1c is > 8.0% but ≤ 9.5%, metformin (minimum dose required: 1,000 mg/day for metformin) and/or a sulfonylurea (minimum dose required: glimepiride 2 mg once daily) will be added, or doses maximized, during the first 2 weeks of the lead-in period. The baseline visit to initiate lanifibranor (V4; Time 0 or randomization visit) will be not sooner than 8 weeks from diabetes medication titration and the patient should have an HbA1c ≤9.0% to proceed to randomization (V4). In addition, if both metformin and glimepiride (or another sulfonylurea) are already maximized at study entry (or the patient is intolerant to either) and the HbA1c ≥ 9.0% but ≤9.5%, we will add sitagliptin 100 mg daily (or an equivalent dose of another DPP-IV inhibitor) to reach an HbA1c ≤9.0% to proceed to randomization (V4).

Afterwards, patient's metformin and/or sulfonylurea dose and/or sitagliptin dose will be maintained at the new stable dose. The baseline visit to initiate lanifibranor (V0; Time 0 or randomization visit) will be not sooner than 8 weeks from diabetes medication titration and the patient should have a HbA_{1c} ≤9.0% to proceed to randomization (V0).

Of note, due to COVID-19 pandemic, in order to be able to accommodate the follow-up study procedures (i.e. liver MRI at V10 and insulin clamp at V11), for already enrolled subjects, treatment may have to be extended by one week up to no longer than 8 weeks.

4.2.1.1 Intrahepatic Triglycerides (IHTG)

This will be the primary endpoint as assessed by ^{1}H-MRS (to be performed at Day -7).

4.2.1.2 Metabolic Studies

As in prior trials by our group (1,2,9,10) to be done between Days -7 and 0.

- Determination of hepatic insulin sensitivity, gluconeogenesis, and DNL. As described below, this will be done with use of labeled glucose, deuterium labeled water (D2O). Combined with a low- and high- dose insulin infusion during the euglycemic hyperinsulinemic clamp (to assess hepatic, muscle and adipose tissue insulin sensitivity) (see Appendix D) with standard stable isotopes to measure glucose and lipid turnover and

substrate oxidation (with indirect calorimetry).

- Glycemic control: HbA1c (Day 0).
- Biomarkers of adipose tissue metabolism (i.e., plasma adiponectin and adipokine panels measured by the gold-standard Millipore multiplex platform). (Day 0)

4.2.1.3 Surrogate Imaging and Plasma Biomarkers of Hepatic

These will be measured by several techniques:

- Vibration-controlled transient elastography (Fibroscan) (3): (Day-42)
- Two-dimensional magnetic resonance elastography (MRE) (4). To be done during the IHTG ^{1}H-MRS measurement. To be done at Day -7.
- T1 MRI mapping (5): To be done at Day -7.
- Plasma biomarkers of liver fibrosis: Established (cytokeratin CK-18, plasma pro-C3 To be done between. Day – 7 and Day 0.

4.2.1.4 Genetic Markers

Performed to assess potential subgroups ("responders") to lanifibranor response (PNPLA3, TM6SF2, others). To be done at Day -7.

4.2.1.5 Description of Methods

Liver ^{1}H-MRS , 2D-MRE and T1 MRI mapping: Between days -14 and 0, subjects will be invited to come to the National High Magnetic Field Laboratory at our university where the 3T magnet is located to have liver fat (IHTG) and liver fibrosis (by 2D-MRE and T1 MRI mapping) measured after at least a 3 hour fast.

Admission for the determination of hepatic insulin sensitivity, gluconeogenesis, and de novo lipogenesis (DNL): Between Day -7 and 0 (to allow scheduling flexibility), subjects will be admitted to the research unit in the afternoon (4:00PM). Glucose and metabolism and DNL rates will be measured as reported in the literature before (1,2,9,10,12). In brief, patients will receive a standardized dinner and will fast overnight for at least 10 hours. Subjects will be given an oral dose (350 ml) of 70% deuterium labeled water (D2O), between 5 PM and midnight and prior to the metabolic experiments on the next day. After 6:00 PM, no calories or caffeine will be allowed until the end of the study on day 2. Non-caloric beverages will be allowed.

If you are unable or unwilling to spend the night in the hospital, there is a possibility to perform this test without the overnight stay. You will still need to come to the CRC the day before the procedure at ~4:00 to 7:00PM to have a blood test done and receive the heavy water that you will drink at home (following the same instructions as if you were admitted). If you choose not to stay overnight you will need a driver the day of the procedure as the heavy water can produce some dizziness.

The day of the procedure we will start at ~5:00-6:00AM. A bolus of [6,6-2H2] glucose (4.8 mg/kg body weight) will be given at 6:00 AM on day 2 followed by a constant infusion (0.08 mg/kg body weight/min) until the end of the study. Indirect calorimetry will be performed with a ventilated hood starting at 8:00 AM on day 2 and at regular intervals. Baseline endogenous glucose production (EGP) will be measured 150-180 minutes after starting [6,6-2H2] glucose to allow time for steady state enrichment of plasma glucose following standard principles of stable isotope dilution techniques. After baseline glucose and lipid turnover measurements, subjects will undergo a two-step euglycemic insulin clamp with a low- and high-dose insulin infusion combined with substrate oxidation determinations (i.e., indirect calorimetry) (see Appendix D).

4.2.2 Intervention Period (24 weeks)

4.2.2.1 Intrahepatic Triglycerides (IHTG)

This will be the primary endpoint as assessed by ^{1}H-MRS (to be performed at V10).

4.2.2.2 Metabolic Studies

As in prior trials (1,2,6) to be done atV11.

- Determination of hepatic insulin sensitivity, gluconeogenesis, DNL. As described below, this will be done with use of labeled glucose, deuterium labeled water (D2O). Combined with a low- and high- dose insulin infusion during the euglycemic hyperinsulinemic clamp (to assess hepatic, muscle and adipose tissue insulin sensitivity) with standard stable isotopes to measure glucose and lipid turnover and substrate oxidation (with indirect calorimetry).
- Glycemic control: HbA1c, advanced lipid testing. (V11).
- Biomarkers of adipose tissue metabolism (i.e., plasma adiponectin and adipokine panels measured by the gold-standard Millipore multiplex platform). (V11).

4.2.2.3 Surrogate Imaging and Plasma Biomarkers of Hepatic Fibrosis

These will be measured by several techniques:

- Vibration-controlled transient elastography (Fibroscan) (3): An established technique that allows to monitor fibrosis non-invasively at the bedside and outpatient setting. (V11).
- Two-dimensional magnetic resonance elastography (MRE) (4). To be done during the IHTG ^{1}H-MRS measurement. To be done at V10.
- T1 MRI mapping (5): A novel scanning protocol that allows for a complementary non-invasive measurement of liver fibrosis (in collaboration with the Oxford laboratory of R. Banerjee et al). To be done at V10.
- Plasma biomarkers of liver fibrosis: Established (cytokeratin CK-18, HA, TIMP-1) and novel (pro-C3) plasma will be tested to gain insights into the role of treatment on liver fibrosis using surrogate markers of disease. To be done at V11.

4.2.3 Off-study Drug Follow-up Period (4 weeks)

After all 24 week procedures, a 4-week safety period of observation will follow to ensure that patients are stable and the patient has a follow-up with their PCP and/or endocrinologist.

4.2.4 Patient Management at the End of Treatment

The trial treatment is stopped after V11.

After the follow-up, the investigator/hepatologists/general practitioner will decide, according to each patient, the need to use the lifestyle changes recommendations whenever appropriate and treatment of comorbidities.

If the study is positive there will be further trials for which these patients may be eligible.

4.2.5 Total Study Duration

The total time (from first patient enrolled to last patient finished) will be 32±4 weeks (4-6 weeks for run-in, 24 weeks of treatment and 4 weeks post-study follow-up), with an estimated recruitment period of 32-40 weeks (conservatively set at ~1-2 patients per week, including about 30% of patients that will not qualify [n=16-20] and about 10 % dropouts/intolerant to lanifibranor that require additional recruitment [n=8].

Of note, due to COVID-19 pandemic, in order to be able to accommodate the follow-up study procedures (i.e. liver MRI at V10 and insulin clamp at V11), for already enrolled subjects, treatment may have to be extended by one week up to no longer than 8 weeks. After all procedures are completed and subjects are off drug, an additional 4-week safety period of observation will follow as specified in section 4.2.3.

4.3 Study Population and Inclusion/Non-inclusion Criteria

We propose to randomize 34 otherwise healthy overweight or obese patients with uncontrolled T2DM (HbA1c ≥ 6.0% to ≤ 9.5%) and NAFLD on imaging (see section 8).

Ten healthy non-obese subjects without NAFLD will also be studied as "normal controls" for all the metabolic and imaging tests to be performed (V1, V3 and V4). We will study them only to examine the response of a person without diabetes to the study tests to be performed in the patients with type 2 diabetes who are participating in the clinical trial. In other words, they will be a "healthy control" to compare the results of blood tests, metabolic studies and imaging studies to be done in patients with diabetes participating in the study. Inclusion/Exclusion for the healthy controls will follow those noted in the protocol for patients with diabetes receiving treatment except that they will not have Type 2 diabetes based on a hemoglobin A1c and will be non-obese, BMI < 30 kg/m^2.

The diagnosis of NAFLD on imaging will be done by measuring intrahepatic triglyceride content (IHTG) using the gold-standard magnetic resonance and spectroscopy (^{1}H-MRS) technique. Pregnant women, prisoners, institutionalized individuals, or others who may be considered vulnerable populations will be excluded. The ethnic mix will reflect the base population in the North Florida/Alachua County area is 70-75% Caucasian, 15-20% African-American, 5-10% Hispanic, and 5% other ethnicities. We will only study otherwise healthy subjects with T2DM based on medical history, physical exam, and blood chemistries and hematologic tests. Body weight (≤ 5%) and physical activity should have been stable for at least 3 months. After informed consent has been obtained, each subject will undergo screening evaluations within the 4-6 weeks prior to the planned first double-blind study drug dose. Subjects may be eligible for randomization if the FPG ≥ 100 mg/dL and ≤ 250 mg/dL) at the Week -6 visit, and meet all other eligibility criteria (including Day -28 fasting fingerstick glucose ≥ 100 mg/dL and ≤ 250 mg/dL).

4.3.1 Inclusion Criteria

1. Be able to communicate meaningfully with the investigator and legally competent to provide written informed consent
2. Have an age between 21 to 75 years inclusive
3. Subjects should be on stable standard of care and background therapy for ongoing chronic conditions, including stable doses of anti-diabetic medications, for at least two (2) months prior to trial entry
4. Have uncontrolled diabetes with a fasting plasma glucose (FPG) ≥ 100 mg/dL but ≤ 250 mg/dL and HbA1c ≥ 6.0% but ≤ 9.5%, on diet alone, or on metformin (≥1,000 mg/day), and/or sulfonylurea and/or DPP-IV therapy SGLT2 inhibitors. These medicines will be continued at stable doses during the entire study.
    - Subjects with an HbA1c > 8.0% but ≤ 9.5% will have their metformin (minimum dose required: 1,000 mg/day) maximized to 1,000 mg BID and/or glimepiride 2 mg once daily added during the first 2 weeks of the run-in period. The baseline visit to initiate lanifibranor (V4; Time 0 or randomization visit) will be not sooner than 8 weeks from diabetes medication titration and the patient should have an HbA1c ≤9.0% to proceed to randomization (V4).
    - In addition, if both metformin and glimepiride (or another sulfonylurea) are already maximized at study entry (or the patient is intolerant to either) and the HbA1c ≥ 9.0% but ≤9.5%, we will add sitagliptin 100 mg daily (or an equivalent dose of another DPP-IV inhibitor) to reach an HbA1c ≤9.0% to proceed to randomization (V4).
5. Presence of hepatic steatosis (Intrahepatic Triglycerides [IHTG]) > 10 % determined by Magnetic Resonance and Spectroscopy (1H-MRS).

6. Have no new symptoms associated with decompensated diabetes in the previous three (3) months.
7. Compensated liver disease with the following hematologic and biochemical criteria on entry into protocol:
    - Hemoglobin > 11 g/dL for females and > 12 g/dL for males
    - White blood cell (WBC) > 2.5 K/µL
    - Neutrophil count > 1.5 K/µL
    - Total bilirubin ≤ 1.3 mg/dL (≤ 22.2 µmol/L). Patients with bilirubin ≤ 1.3 mg/dL can be included if non-conjugated bilirubin in the setting of a Gilbert's syndrome.
    - Albumin > 36 g/L
8. No other causes of chronic liver disease (autoimmune, primary biliary cholangitis, HBV, HCV, Wilson's, α-1-antitrypsin deficiency, hemochromatosis, other).
9. Negative pregnancy test or at least two-year post-menopausal. Women with childbearing potential (i.e. fertile, following menarche and until becoming post- menopausal unless permanently sterile) must be using a highly effective method of contraception (i.e. combined (estrogen- and progesterone-containing) hormonal/ progesterone-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner). The contraceptive method will have to be followed for at least one menstruation cycle after the end of the study.

4.3.2 Non-Inclusion Criteria

1. Evidence of liver disease other than NAFLD.
2. History of excessive alcohol intake, defined by ≥ 21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to enrollment, where a "unit" of alcohol is equivalent to 12-ounce beer, 4-ounce glass of wine, or 1 ounce shot of hard liquor.
3. Unstable metabolic condition: Weight change > 5% in the 3 months prior to enrollment, diabetes with poor glycemic control (HgbA1c > 9.5% or FPG > 250 mg/dl), introduction of an anti-obesity drug/malabsorptive or restrictive bariatric (weight loss) surgery in the past 6 months prior to screening.
4. History of gastrointestinal malabsorptive bariatric surgery within less than 5 years or ingestion of drugs known to produce hepatic steatosis including corticosteroids, high-dose estrogens, methotrexate, tetracycline or amiodarone in the previous 6 months.
5. Subjects on sulfonylureas, metformin, GLP-1RA or DPP-IV unless the dose and body weight (within 5%) have been stable for at least two (2) months prior to study entry.
6. Patients on insulin, pioglitazone (or prior use in the past 12 months).
7. Patients on any of the following medications unless the patient has been on stable doses of such agents for the past two (2) months before entry into the study: thiazide or furosemide diuretics, beta- blockers, or other chronic medications with known adverse effects on glucose tolerance levels. Patients may be taking stable doses of estrogens or other hormonal replacement therapy if the patient has been on these agents for the prior two (2) months. Patients taking systemic glucocorticoids will be excluded.

   Patient on treatment with strong inducers or inhibitors of CYP2C8, or treatment with substrates of CYP2B6 or CYP2C8. When administered chronically, they should be replaced 2 months before the trial entry (See Inclusion criteria #3). If not administered chronically, they should be stopped at least 7 days before first dosing.

8. Patients with:
    a. History of myopathies or evidence of active muscle diseases
    b. Unstable cardiovascular disease, including:
        i. Unstable angina (i.e., new or worsening symptoms of coronary heart disease within the past 3 months), acute coronary syndrome within the past 6 months, acute myocardial infarction in the past 3 months or heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months
        ii. History of (within prior 3 months) or current unstable cardiac dysrhythmias
        iii. Uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg.
        iv. Stroke or transient ischemic attack within the prior 6 months
    c. History of malignancy in the past 5 years and/or active neoplasm with the exception of resolved superficial nonmelanoma skin cancer
    d. History of bladder disease and/or hematuria or has current hematuria unless due to a urinary tract infection
    e. Any of the following laboratory values:
        i. Serum bilirubin > 1.3 mg/dL (or > 22.2 µmol/L). Patients with bilirubin > 1.3 mg/dL can be included if non-conjugated bilirubin in the setting of a Gilbert's syndrome.
        ii. Serum ALT > 3X ULN
        iii. INR > 1.2
        iv. Platelets < 150,000 per microliter of blood
        v. Renal impairment as demonstrated by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m2
        vi. Total creatinine kinase > 1.5 X ULN
        vii. Lipase > ULN
        viii. Hemoglobin A1c > 9.5%
9. Significant systemic or major illnesses other than liver disease, including those listed in exclusion criteria #8 and pulmonary disease, organ transplantation, serious psychiatric disease, that, in the opinion of the investigator, would preclude treatment with lanifibranor and/or adequate follow up.
10. HB antigen > 0, HCV > 0 (patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years), prior history of HIV infection.
11. Pregnancy/lactation or inability to adhere to adequate contraception in women of child-bearing potential.
12. Any other condition which, in the opinion of the investigator would impede competence or compliance or possibly hinder completion of the study.
13. Body mass index (BMI) > 45 kg/m2.
14. Type 1 diabetes and type 2 diabetic patient on insulin.
15. Diabetic ketoacidosis.
16. Fasting plasma triglycerides > 500 mg/dL.
17. Hemostasis disorders or current treatment with anticoagulants.
18. Participation in any other investigational drug study within the previous 3 months.

19. Have a known hypersensitivity to any of the ingredients or excipients of the IMP including: Lactose monohydrate, hypromellose, sodium lauryl sulphate, sodium starch glycolate, magnesium stearate, Opadry™ II 85F18422, DSS Granular, cellulose microcrystalline, maize starch.
20. Be possibly dependent on the Investigator (e.g., including, but not limited to, affiliated employee).
21. Osteopenia or any other well documented bone disease. Patient without well documented osteopenia treated with vitamin D and/or calcium based supplements for preventive reasons can be included.
22. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of investigator.
23. Metallic implant of any sort that prevents MRI examination including, but not limited to: aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, tattoo, body piercing that cannot be removed, cochlear implant; or any other contraindication to MRI examination.

4.3.3 Prohibited Concomitant Medications

- PPAR gamma agonists, PPAR alpha agonists (fibrates), ezetimibe,
- Bile salts chelators, Phytosterols, fish oils,
- Insulin,
- Vitamins E (alpha-tocopherol),
- Anticoagulants (incl. warfarin, dabigatran, rivaroxaban, apixaban),
- Systemic steroids (greater than physiological replacement of 30 mg of hydrocortisone or equivalent per day).
- Substrates of CYP2B6 (e.g. artemether, artemisinin, bupropion, coumarins [e.g. warfarin, acenocumarol], cyclophosphamide, efavirenz, ifosfamine, mephobarbital, methadone, nevirapine, pethidine, propofol, selegiline). However, if medically necessary, these treatments can be administered for a single intake, occasionally.
- Substrates of CYP2C8 (e.g. amodiaquine, clopidogrel, daprodustat, dasabuvir, enzalumatide, montelukast, paclitaxel, repaglinide, torasemide). However, if medically necessary, these treatments can be administered for a single intake, occasionally.
- CYP2C8 strong inducers (e.g. pentobarbital, phenytoin, rifampin, rifamycin, secobarbital). However, if medically necessary, these treatments can be administered for a single intake, occasionally.
- CYP2C8 strong inhibitors, when systemically administered, i.e. by oral, intra-venous or intra-muscular route of administration (e.g. gemfibrozil, clopidogrel, felodipine, zafirlukast, candesartan celixetil, ketoconazole).

Allowable medications for standard care or precautions:

- ***Obesity***: stable weight defined by no more than a change of >5% in the 3 months prior to enrollment (see exclusion criteria N° 3).
- Treatment used for the underlying medical conditions:

  Treatments are allowed within certain restrictions (described above and below) and provided that they have been kept at ***stable doses for at least 2 months before inclusion in the study***.
  - Type 2 diabetes:

- Metformin,
- Sulfonylureas,
- Dipeptidyl peptidase-4 inhibitors,
- Sodium-glucose transport protein 2 inhibitors: canagliflozin, dapagliflozin and empagliflozin.

- ***Hyperlipidemia***: only statins at stable doses will be allowed.
- ***Antiplatelets agents:*** The antiplatelets agents (incl. low-dose aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor) are allowed.
- ***Herbal supplements:*** Herbal preparations or vitamin supplements should not be taken as it is difficult to know exactly what they contain and could be liver toxic.

- ***Other Medications***

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

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

4.3.4 Enrollment

If a patient is not eligible, the main reason for non-inclusion will be documented in the source document and the screening log. After eligibility is confirmed, patients will be assigned a treatment number. Treatment numbers will be allocated in ascending order, the order in which patients are included. The investigator or a staff member will enter the patient initials and number in a web-based electronic case report form (eCRF), the confidential patient identification list and the drug dispensing log.

4.4 Study Medication

4.4.1 Identity of Investigational Medicinal Product(s) (IMP)

The lanifibranor tablets and placebo to match (PTM) are white to off-white, oval shape, bi-convex, film-coated tablets:

- Each active tablet contains 400 mg of the active substance lanifibranor in an immediate release formulation. The chemical name of the active substance is (4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloro-1H-indol-2-yl]butanoic acid).
- The placebo tablet contains a physical mixture of lactose monohydrate, microcrystalline cellulose, and pre-gelatinized starch and magnesium stearate.

4.4.2 Treatments Administered

This double blinded placebo-controlled study involves a therapeutic dose of 800 mg lanifibranor (QD).

The lanifibranor tablets and PTM are packaged into round high-density polyethylene (HDPE) bottles containing 38 tablets for a treatment period of one month, plus a use margin of 1 week with proper closures fitted with a silicagel cartridge. Two bottles each (either active or placebo) are assembled in a carton to compose monthly Kits as detailed below:

- Placebo Kit: Morning (P+P)
- 800 mg Kit: Morning (A+A)

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

A total of 6 monthly patient kits (2 HDPE Bottles of 38 tablets each) is representing the treatment per patient for the clinical study.

4.4.3 Medication Dispensing

4.4.3.1 Medication Dispensing

The patients receive 3 monthly patient kits at V4 and 3 monthly patient kits at V6. They are instructed to take morning 2 tablets with food, i.e. one tablet from either the one of the two containers. The overall treatment duration is 24 weeks. However, due to COVID-19 pandemic, in order to be able to accommodate the follow-up study procedures (i.e. liver MRI at V10 and insulin clamp at V11), for already enrolled subjects, treatment may have to be extended by one week up to no longer than 8 weeks. Additional medication dispensing, if necessary, will be done as part of an unscheduled follow-up visit.

Dosage modifications are not permitted. Should the patient or the investigator for any reason wish to discontinue treatment, they may do so at any time. The date of the last dose and any dosage modifications by the patient are documented in the eCRF.

4.4.4 Selection and Timing of Dose for Each Patient

Patients will be randomized equally 1:1: to either dose of lanifibranor or placebo.

The randomization list will be setup with blocs of size equal to 4.

The randomization list will be produced by a statistician of Keyrus Biopharma according to their SOPs and will be used to prepare the medication accordingly. Each eligible subject will be randomized to placebo or lanifibranor according to the randomization scheme at the time of randomization visit (V4).

Treatment numbers will be allocated in ascending order using the next available consecutive number.

One copy of this list will be sent to the company responsible for manufacturing and labelling of the treatment (AMATSI) and another blind copy will be sent to the investigator. These copies will be stored in confidential manner up to the unblinding after database lock.

The blind copy will contain three additional columns and the investigator will have to complete the columns “Randomization date”, “Patient number” and “Investigator initials” after each randomization.

Two separate sealed envelopes (one for the investigator, one for STRAGEN) will be prepared by Keyrus Biopharma. These individual envelopes will contain the identity of the study medication allocated to the patient in case of emergency (see §9.2.1).

4.4.5 Labeling

Packaging and labeling is performed by Amatsi group, 17 Rue des Vautes, 34980 Saint-Gély-du-Fesc, France Phone: +33 (0) 4 99 58 38 60.

The immediate containers (bottles) and the outer packaging (medication boxes) will contain the information required by national regulations.

Table 4. Summary of Labeling Details

Caution: New Drug--Limited by Federal (or United States) law to investigational use.
Investigator site Division of Endocrinology, Diabetes and Metabolism

Pharmaceutical dosage form	The University of Florida 38 tablets of lanifibranor 400 mg or Placebo to Match. For Oral Use
Batch N°:	XXXX
Bottle ID:	XXXX
Kit N°:	XXXX
Protocol ID:	*Lanifibranor /2018*
Principal Investigator:	Kenneth Cusi, M.D.
Direction for Use:	Take 2 tablets by mouth once daily with food (morning), from either one of the two bottles.
For Clinical Trial Use Only	Return all empty bottles or unused medication to the trial Centre at the next visit.
Storage :	Store in original container at 25°C or below.
Keep Out of Reach of Children.	

4.4.6 Accountability

The investigator will maintain accountability records showing the quantities of IMP received at the study site and dispensed to each patient. Any unused IMP, including empty or partially used containers, will be accounted for and then destroyed. At the time of destruction, the investigator must verify that all unused or partially used investigational medicinal product supplies have been returned by the clinical study subject and that no remaining supplies are in the investigator's possession.

4.4.7 Treatment Compliance

The investigator will maintain accountability records showing the quantities of IMP received at the study site and dispensed to each patient. Any unused IMP, including empty or partially used containers, will be accounted for and then destroyed. Treatment Compliance

The following means will be taken to improve compliance to treatment:

- the investigator will attempt to select patients able to understand and to comply with instructions,
- the patient should be instructed to return containers at the end of the treatment period,
- remaining tablets will be counted by the Site Coordinator and recorded in the eCRF

4.4.8 Return or Destruction of Investigational Products

The products are collected by the Principal Investigator at the end of the study and are thereafter destroyed.

5 Measurements Assessed and Study Flow Chart

The following section presents the assessments performed at each visit. Target dates are ±5 days compared to V1.

5.1 Table of Study Procedures and Assessments

A table is provided in the Schedule of Study Procedures (Table 1).

5.2 Specific Procedures for Assessment of Outcomes

Safety laboratories should be monitored by a central laboratory in real time with potential DILI alerts sent to the investigator.

If patient lives in a remote area, testing can be performed locally and the results communicated to the investigator site promptly.

5.2.1 Urine Samples

Urine Samples will be collected at V1, V11 and V12.

Urine Pregnancy test will be performed at V1, V4, V7, V9, V11 and V12.

Urine specimens will be obtained by providing participants with a collection cup and instructions for collecting as described in the sampling kit supplied by the hospital laboratory.

Safety assessments may be performed on the urine samples in case of renal function impairment is observed during the study. Increase of 50 % or 1.5. Albuminuria and other biomarker like cystatin C will be tested, and aliquots of urine samples will be stored in case where a urine

biomarker specific of NAFLD would be validated during the study.

The tube labels need to contain the following information: Study Site, Subject Number, Day, Time, Visit number

All urines samples will be destroyed by the hospital laboratory at the end of a scheduled storage period (1 year after the end of the study).

5.2.2 Blood Samples Taken

Blood sample taken are performed at V1 (screening), V4 (randomization), V5, V6, V7, V8, V9, V11 and V12 (Follow-up).

Total blood volume sampled during the study for each patient (for, biomarkers, safety and efficacy biological tests) will be as follows:

Table 5. Blood Volume Taken at Each Visit per Type

(ml)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
SST	5			5							5	
Serum (red)	1.8			6.8	1.8	1.8	1.8	1.8	1.8		6.8	6.8
EDTA (whole blood)	2			2	2	2	2	2	2		2	2
EDTA (plasma)				154			6				154	
Citrate	2.7			2.7	2.7	2.7	2.7	2.7	2.7		2.7	2.7
Fluoride	2										2	2
Li Hep	6			3	3		3				6	3
Glucose ANALOX				25							25	
Total (ml)	**19.5**			**198.5**	**9.5**	**4.5**	**15.5**	**4.5**	**4.5**		**203.5**	**11.5**

OVERALL TOTAL: 471.5 ml

Attention must be paid to the kind of blood sample required as they vary between visits.

For the monitoring of the individual subject, each sample should be collected under the same conditions (e.g. time ± 1h) as the baseline sample. This is to overcome the effects of the circadian variation of the biomarkers measured.

All blood samples will be destroyed by the laboratory at the end of a scheduled storage period (1 year after the end of the study).

5.2.3 Waist Measurement

The Waist measurement must be done at midway between the top of the hip bone and the bottom of the ribs during a normal breath-out (Appendix B: Methods and Normal Values for Vital Signs, Waist and ECG).

5.2.4 Electrocardiogram

12-lead ECGs will be performed at Screening (V1), and the end-of-treatment visit (V11).

5.2.5 Vital Signs

Blood pressure will be measured by using a sphygmomanometer. The results will be recorded in millimeters of mercury (mmHg). Pulse rate will be measured for 30 seconds and will be recorded as beats/minute. Blood pressure and pulse will be measured lying after at least a 10-minute rest.

5.3 Procedures at Each Visit

5.3.1 Screening (V1)

The Principal Investigator invites the potential patients to participate to the study according to the patient's medical records. Both will go through the informed consent and the Principal Investigator answers to any question the patient would have.

The patient is given enough time to discuss his/her participation to the study with his/her family, friends and family doctor.

The patient is asked to date and sign the "Informed consent form", prior to any study procedure.

Screening (V1) procedures are listed on the "Study Schedule of Procedures". (see Table 1)

Medical history including concomitant medication is reviewed.

Physical examination (vital signs, weight, height and waist measurement) is performed.

12-lead ECG, routine chemistries (CBC, CMP, lipids, CPK, CPK-MB, HbA1c) and urinalysis (including urine pregnancy test) are performed.

TSH, free T4, not necessary if available within the past 12 months.

Fibroscan procedures: CAP and VCTE are performed.

In subjects with abnormal labs, baseline measure (BLM) should be determined by 2 separate measurements obtained approximately approximately 4 weeks apart. To be eligible for study entry, the differences in the levels of those repeat measures of baseline serum AST, ALT, ALP, and total bilirubin should be small (<20%).

Subjects with an HbA1c > 8.0% but ≤ 9.5% will have their metformin (minimum dose required: 1,000 mg/day for metformin) maximized to 1,000 mg BID and/or glimepiride 2 mg once daily added during the first 2 weeks of the run-in period.

In addition, if both metformin and glimepiride (or another sulfonylurea) are already maximized at study entry (or the patient is intolerant to either) and the HbA1c is ≥ 9.0% but ≤9.5%, sitagliptin 100 mg daily (or an equivalent dose of another DPP-IV inhibitor) will be added.

All patients on concomitant anti-diabetic medications should have, or be provided with, a glucose monitor and instructions for its use. Fasting blood glucose and spontaneous measurements in the event of suspected hypoglycemia should be routinely monitored by the patient and values should be recorded (in their glucose monitoring device or diaries) to be discussed at each visit with study staff. Patients will be instructed on actions to take in the event of hypoglycemia in accordance with standard of care.

Finally, eligibility criteria are reviewed and if the patient is eligible, the next visit should take place within 2 weeks +/- 5 days.

5.3.2 Medication Titration (V2) at Week -4

The assessments performed are listed on the "Study Schedule of Procedures" (see Table 1).

The key procedure at this visit is the DM medication titration done by staff, with assessment including a fasting fingerstick glucose procedure.

AEs, if any occurred since the previous visit, are reported. Please refer to section 6 for AEs reporting.

5.3.3 Baseline Visit (V3) at Week -1

The procedures are listed on the "Study Schedule of Procedures" (see Table 1).

Liver imaging: liver fibrosis (MRE) and T1 MR mapping and liver IHTG content are performed.

AEs, if any occurred since the previous visit, are reported. Please refer to section 6 for AEs reporting.

5.3.4 Randomization Time 0 (V4)

The assessments to be performed are listed on the "Study Schedule of Procedures". (see Table 1)

At this visit, the eligibility of the patient is confirmed (inclusion/exclusion criteria).

Patient will be admitted to the CRC (clinical research unit) including overnight stay.

Inpatient metabolic testing will be performed: insulin sensitivity study, DNL and GNG.

Blood sampling using kits and instructions provided will be done for safety and efficacy purposes. Blood samples will be taken in the morning after overnight fasting. The patient must be fasting overnight from 10:00 pm.

AEs, if any occurred since the last visit, are reported. Please refer to section 6 for AEs reporting

Concomitant medications are also reported.

The patients are then randomized and receive 3 monthly patient kits of medication. Each kit will contain 2 bottles. Each kit contains 4-weeks plus 1-week margin of tablets.

Patients are carefully instructed to take morning 2 tablets with food, i.e. one tablet from either container.

Patients are also carefully instructed to come back to the site in case of symptoms of dyspnea, edema, or a presumptive diagnosis of heart failure. NT-proBNP should be measured as close to the event as possible. They will also be instructed to call the investigator in case of new or worsening symptoms of clinical hepatitis, including loss of appetite, fatigue, mild fever, muscle or joint aches, nausea and vomiting. This will be reminded to them at each subsequent visit. Patients and caregivers accompanying them during the study visits will receive education for potential symptoms of adverse effects that should be reported to the investigators, such as skeletal muscle pain, weight gain, peripheral edema, shortness of breath, or new or worsening symptoms of clinical hepatitis (RUQ pain, dark urine, extreme fatigue, nausea and vomiting), mild fever, etc. These will be asked and recorded at each visit.

Important is to remind the patients, to bring back the unused medication at each visit.

5.3.5 Follow-up Visits (V5) at Week 4, (V6) at Week 8, (V7) at Week 12, (V8) at Week 16 and (V9) at week 20

The assessments to be performed are listed on the "Study Schedule of Procedures". (see Table 1)

Please note that the follow-up visits are not at regular intervals and the assessments vary from one

visit to the next.

Blood sampling using kits and instructions provided will be done for safety and efficacy purposes.If subjects develop elevations of AST or ALT > 2 times baseline measure or total bilirubin > 1.5 times BLM while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2-3 times per week with or without drug discontinuation.

AEs, if any occurred since the previous visit, are reported. Please refer to section 6 for AEs reporting. At each visit, the investigator will ask the patients on the occurrence of skeletal muscle pain or joint aches, peripheral edema, shortness of breath, loss of appetite, fatigue, mild fever, nausea and vomiting since last visit.

Concomitant medications are recorded.

If 2 months after randomization, i.e. (V6) at Week 8, sitagliptin 100 mg/day will be added the HbA1c exceeds ≥9.5%. If the subject is already on sitagliptin (or an equivalent dose of another DPP-IV inhibitor), or has a history of intolerance to DPP-IV inhibitors, bedtime long-acting insulin Lantus at 0.3 units/kg will be started and titrated aiming to keep the fasting plasma glucose below 120 mg/dL. If at 4 months, i.e. (V8) at Week 16, the HbA1c remains ≥9.5% and the patient is already on maximal doses of metformin, sulfonyurea and sitagliptin, as well as on insulin, the patient will be discontinued from the study due to non-adherence to therapy.

At V7, patient receives 3 monthly patient kits of medication. Each kit will contain 2 bottles. Each kit contains 4-weeks plus 1-week margin of tablets.

For affected subjects due to COVID-19 pandemic, in case drug treatment has to be extended for 1-8 weeks, additional safety labs (CBC, CMP, CK, and lipase) if not available in the past 8 weeks, will have to be re-collected prior to the treatment extension. Additional medication dispensing if needed will be performed in an unscheduled visit. If any adverse reaction occur during this period patient will be seen in an unscheduled visit as needed.

5.3.6 Repeat Baseline Studies (V10) at Week 23 and at (V11) at Week 24

The assessments to be performed are listed on the "Study Schedule of Procedures" (see Table 1).

The assessments are different in V10 and V11 (see below).

Blood sampling using kits and instructions provided will be performed for safety and efficacy purposes.

Key procedures at each visit are the following:

At (V10) liver imaging: liver fibrosis (MRE) and T1 MR mapping and liver IHTG content are performed.

At (V11) patient will be admitted to the CRC (research unit) including an overnight stay.

Inpatient metabolic testing is performed: including HbA1c, insulin sensitivity study, DNL and GNG.

AEs, if any occurred since the previous visit, are reported. Please refer to section 6 for AEs reporting.

Concomitant medications are recorded.

As already noted, due to COVID-19 pandemic, for already enrolled subjects, the liver MRI at V10 and insulin clamp at V11 may have to be completed out of window by one week and up no longer than eight weeks.

5.3.7 Off-Drug Follow-up (V12) at Week 28

This last patient's visit includes: concomitant medications and AEs reporting, vital signs, routine

chemistries, urinalysis and urinary pregnancy test among other assessments.

All the assessments to be performed are listed on the "Study Schedule of Procedures". (see Table 1).

For those subjects where the course of the study was affected by the COVID-19 pandemic, and treatment was extended for no longer than 1-8 weeks, the final off-drug follow-up visit 12 will be performed 4 weeks after stopping the study drug.

5.3.8 Unscheduled/Safety Visits

During the all treatment and the follow-up period, the investigator may conduct unscheduled visit that may perform again study procedures, including vital signs assessments, blood sample taken and physical examination. These visits will have to be motivated by the investigator in the aim of guarantee the safety of the patients.

Specific events listed below will automatically generate an unscheduled/safety visit:

- If patients develop elevations of AST or ALT > 2 times baseline measure or total bilirubin > 1.5 times BLM while on study, testing should be repeated within 48 to 72 hours. Persistent elevations should be followed by repeat testing and physical examination 2-3 times per week with or without drug discontinuation.
- If a patient has symptoms of dyspnea, edema, or a presumptive diagnosis of heart failure, NT-proBNP should be measured as close to the event as possible.
- Asymptomatic subjects with lipase values above 1.3X ULN (if not on a DPP-IV inhibitor) or >2.0X ULN if taking a DPP-IV inhibitor, will be retested within 7 days without drug interruption. Should retest values return to below inclusion criteria, the drug may be continued. If retest values are > ULN or the subject becomes symptomatic, they should be discontinued from drug.

Please also refer to section 9.1 for patient withdrawal criteria.

6 Safety Assessment

6.1 Adverse Events

All adverse events (AEs), regardless of severity or potential relationship to study drug, will be recorded using medical terminology in the source document and the eCRF

6.1.1 Definitions

- **Adverse event:** Any untoward medical occurrence in a patient administered the investigational medicinal product (IMP) and which does not necessarily have a causal relationship with the IMP. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the IMP, whether or not considered related to the IMP.
- **Suspected adverse reaction**: Any AE for which there is a reasonable possibility that the IMP caused the AE. All untoward and unintended responses to the IMP related to any dose administered. All AEs judged by the investigator as having a reasonable causal relationship (i.e. unlikely, possible or probable) to the IMP qualify as suspected adverse reactions. The expression "reasonable causal relationship" means there is evidence to suggest a causal relationship between the IMP and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by the IMP.

6.1.2 Collection

The condition of the patients will be monitored throughout the study.

Any AE (including laboratory test abnormalities, patient's subjective symptoms, intercurrent illnesses or injuries, and/or study procedures-related AE) reported spontaneously by the patients, or observed by the investigator or medical staff, will be recorded in the source records and the eCRF.

Any untoward medical event, which occurs from the time of signed Informed Consent to the time of first IMP administration, will be classified as "non treatment-emergent AE. An AE includes:

A clinically relevant worsening of an existing illness and/or a clinical laboratory adverse event (CLAE): a laboratory abnormality that is clinically significant and suggests toxicity of a magnitude that requires active management (either active treatment or more clinical investigations, such as more frequent follow-up to monitor the abnormality.

The following are not to be reported as AEs:

- Pre-existing conditions found at screening or before exposure to trial drug: they should be included instead in the medical history or concomitant procedures.
- Non-severe hypoglycemia is to be considered an AE, but will be reported under hypoglycemic episodes forms rather than in the eCRF AE forms.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened since the participant has signed the informed consent form

6.1.3 Intensity Rating

- The Common Terminology Criteria for Adverse Events (CTCAE: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used for reporting AEs.

  The intensity of an AE will be rated as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL) (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Mild: no interference with the patient's daily activities and does not require mandatory corrective/symptomatic treatment.

- Moderate: moderate interference with the patient's daily activities and/or requires minimal medical intervention or corrective treatment required.
- Severe: major and unacceptable interference with the patient's daily activities and requires mandatory corrective/symptomatic treatment, possible hospitalization.

6.1.4 Causality Rating

The causal relationship of an AE to the IMP will be rated as follows:

- Unrelated: Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable.
- Unlikely: Does not follow a reasonable temporal sequence from administration of the IMP or is most likely related to another etiology than the trial drug such as the patient's clinical state, environmental factors or other therapies.
- Possible: Follows a reasonable temporal sequence from administration of the IMP, and/or a causal relationship cannot be excluded and remains likely.
- Probable: good reason (such as clear-cut temporal association with improvement on cessation of the IMP or reduction in dose, or reappears upon (accidental) rechallenge, or follows a known pattern of response to the IMP) and sufficient documentation to assume a causal relationship.

6.1.5 Action Taken

The action taken with the IMP for an AE will be rated as IMP withdrawn, temporary interruption, or dose not changed. AEs requiring therapy will be treated with recognized standards of medical care to protect the health and the well-being of the patient.

6.1.6 Outcome

The outcome of an AE will be rated as recovered, recovering, sequelae, not recovered, fatal or unknown. The investigator will follow-up any AE until it is resolved or until the medical condition of the patient is stable. All relevant follow-up information will be collected. For AEs that are ongoing at the last visit, the investigator will make thorough efforts to document the outcome.

Definitions:

- Recovered/resolved: The subject has fully recovered, or by treatment of some sort the condition reported has now returned to the level observed at the first trial-related activity after the subject signed the informed consent.
- Recovering/resolving: The condition is improving and subject expected to recover from the mentioned event.
- Recovered/resolved with sequelae: The subject has recovered from AE but with lasting effect due to a disease, injury, treatment or procedure.
- Not recovered: The condition has not improved or the symptoms are unchanged. Also, if the outcome is unknown.
- Fatal: To be used only if the subject has died from the condition/reported adverse event. An AE with fatal outcome must be reported as an SAE.
- Unknown: There is no available information related to the condition of the AE.

6.1.7 Multiple Signs or Symptoms

If an AE consists of several signs or symptoms that can be represented by one single syndrome or diagnosis, the syndrome or diagnosis will be recorded in the eCRF as the AE instead of the individual signs or symptoms.

6.1.8 Worsening Signs

Symptoms, syndromes or diagnoses present before the first IMP administration will be considered as AEs if they worsen after the start of the IMP.

6.2 Serious Adverse Events

6.2.1 Definitions

A Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (at the time of the event);
- requires in patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- or is an important medical event.

Death: the death of a patient enrolled in a clinical study is per se not an event, but an outcome. An AE resulting in a fatal outcome must be fully documented and reported, including if the death occurred after treatment end, and regardless of the causality relationship of the death to the IMP. The cause of the death is usually the AE. If the cause cannot be determined, the case will be considered an unexplained death

Life-threatening: an AE that places the patient, in the view of the initial reporter (investigator), at immediate risk of death from the AE as it occurred, i.e. it does not include an AE that, had it occurred in a more severe form, might have caused death.

Hospitalization: a hospitalization for a diagnosis or therapeutic procedure planned before study enrolment but performed after the enrolment should not be considered for SAE and should be reported in the eCRF in the medical history or concomitant procedures page.

Disability: a substantial disruption of a person's ability to conduct normal life functions.

Important medical event: an important medical event that may not result in death, be life-threatening, or require hospitalization may be considered as a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. The concept includes AEs which suggest a significant hazard, contraindication or precaution for use, occurrence of malignancy or development of drug dependency or drug abuse.

Other events for immediate reporting

Overdose: an overdose of an IMP is the accidental or intentional administration of a dose higher than the highest dose under clinical investigation. An overdose will be documented and reported in an expedited manner with the same procedure and timelines as for SAEs (see section 6.3.1), independently from the occurrence of an AE.

Pregnancy: The occurrence of a pregnancy of a study patient or a partner of a study patient discovered during IMP administration or within 1 week after last administration of the IMP, is to be reported in an expedited manner with the same procedure and timelines as for SAEs (see section 6.3.1), independently from the occurrence of an AE. Specific follow-up of the event will be done by the investigator until pregnancy outcome, following standard procedures established by the University of Florida Institutional Review Board (IRB).

6.3 Reporting requirements

6.3.1 Immediate reporting

The investigator will immediately, i.e. within 24 hours from first knowledge, report any SAE

occurring during the study to the appropriate Data Safety Monitor Board (DSMB) and IRB that approved the protocol.

The investigator will complete sign a SAE Report Form and transmit it to the DSMB and IRB by email or telefax not later than 24 hours after the first knowledge of the SAE. The DSMB and IRB acknowledge the receipt of the SAE information by email to the investigational site within one working day (unless on a weekend or Holiday when reporting will occur on the first working day). In the absence of email acknowledging the receipt, or in case of any issue in sending the fax or email, the investigator shall contact the DSMB and IRB by any means for ensuring the receipt of SAE information at the earliest opportunity.

Any follow-up information will be reported to the DSMB and IRB as soon as it becomes known, with the same process and timelines as described here above for initial reports.

SAEs occurring after the last study visit will only be reported if the investigator believes that the event may have been caused by the IMP or a protocol procedure.

6.3.2 IND safety reporting requirements

The investigator will be responsible for the declaration of suspected unexpected serious adverse reactions (SUSARs) according to US FDA regulation. Expectedness will be based on the safety reference document i.e. the Investigator Brochure (IB).

6.3.3 Reporting to Inventiva SA

Inventiva SA, through its new pharmacovigilance contractor, United BioSource Corporation (UBC), will be copied on all SUSAR and SAE declarations and will collect in its safety database

UNITED BIOSOURCE CORPORATION

Email: Inventivasafety@ubc.com

UBC will ensure that appropriate cross-reporting of SUSAR originating from the present clinical trial is performed in all countries with on-going lanifibranor trials.

6.3.4 Cross-reporting

SUSAR and SAE's occurring from other on-going lanifibranor trials will be sent by Inventiva SA, through its pharmacovigilance contractor, UBC, to the investigator for reporting to local competent authorities in accordance with local regulation.

6.4 Safety Variables

All safety variables will be primary ones. Safety evaluations will be completed as given in section 8.7 and as indicated below.

The investigator will rate all safety variables as to clinical relevance or not. In case of a clinically relevant abnormality, the safety evaluation will be repeated. If the abnormality is confirmed and clinically relevant, it will be recorded as an AE term in the eCRF. The abnormality will be followed up until the value has returned to normal or an adequate explanation is found.

Safety endpoints

Secondary safety endpoints will be used to support the safety objectives of the study, such as the number of treatment-emergent adverse events, including hypoglycemic episodes (i.e., blood-confirmed glucose levels below 40 and 70 mg/dL, severe symptomatic hypoglycaemic episodes during the trial), as well as haematologic and biochemical tests as described in Table 6 below.

Hypoglycaemic episodes will be classified and then summarized as: a) Number and percentage of subjects with at least one event; b) Total number of events and per ADA category (see below); and c) Event rate per 100 patient years of exposure.

The study will use the ADA classification/criteria of hypoglycaemia as follows (35):

- Severe hypoglycaemia: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- Asymptomatic hypoglycaemia: An episode not accompanied by typical symptoms of hypoglycaemia, but with a measured plasma glucose concentration ≤ 70 mg/dL.
- Documented symptomatic hypoglycaemia: An episode during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL.
- Pseudo-hypoglycaemia: An episode during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration > 70 mg/dL but approaching that level.
- Probable symptomatic hypoglycaemia: An episode during which symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL.

6.4.1 Physical Examination

Physical examinations will be conducted by the investigators. Any findings will be documented in the source document and recorded in the eCRF.

6.4.2 Laboratory Tests

Laboratory tests will be analyzed mainly at the hospital laboratory.

Additional samples for laboratory safety variables may be drawn at any time during the study at the investigators judgment. The laboratory assessments performed at each visit are listed in the following table (see Table 6).

Table 6. Laboratory Tests

WEEK	- 6	-4	-1	0	4	8	12	16	20	23	24	28
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
TEST												
Complete Blood Count												
RBC count	X			X	X	X	X	X	X		X	X
Haemoglobin	X			X	X	X	X	X	X		X	X
Haematocrit	X			X	X	X	X	X	X		X	X
WBC count	X			X	X	X	X	X	X		X	X
WBC Differential				X	X	X	X	X	X		X	X
Platelet count	X			X	X	X	X	X	X		X	X
Comprehensive metabolic profile												
Fasting Plasma Glucose	X			X	X	X	X	X	X		X	X
Electrolytes	X			X	X	X	X	X	X		X	X
Albumin	X			X	X	X	X	X	X		X	X
Total protein	X			X	X	X	X	X	X		X	X
Calcium	X			X	X	X	X	X	X		X	X

WEEK	- 6	-4	-1	0	4	8	12	16	20	23	24	28
VISIT	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**
TEST												
Total bilirubin	X			X	X	X	X	X	X		X	X
AST	X			X	X	X	X	X	X		X	X
ALT	X			X	X	X	X	X	X		X	X
Alkaline Phosphatase (ALP)	X			X	X	X	X	X	X		X	X
INR	X			X	X	X	X	X	X		X	X
Serum creatinine and eGFR	X			X	X	X	X	X	X		X	X
Lipase	X			X	X	X	X	X	X		X	X
Lipids												
Total Cholesterol	X			X	X	X	X	X	X		X	X
HDL-C	X			X	X	X	X	X	X		X	X
LDL-C	X			X	X	X	X	X	X		X	X
Non-HDL-C	X			X	X	X	X	X	X		X	X
Triglycerides	X			X	X	X	X	X	X		X	X
CPK and CPK-MB	X			X	X	X	X	X	X		X	X
HbA1C	X		X*	X		X		X			X	X
TSH, Free T4	X											
Serology	X											
Urinalysis	X										X	X
Urine pregnancy test	X			X			X		X		X	X
FSH (postmenopausal patients only)	X											
Outcome Laboratories												
Fasting Plasma Glucose	X				X	X	X	X	X		X	X
Fasting Fingerstick glucose		X					X					
Advanced lipid panel (lipoproteins, particle # size)				X			X				X	
Exploratory biomarkers (hsCRP, IL-6, TGF-beta)				X	X		X				X	
Adiponectin				X			X				X	
ProC3 (Nordic)				X			X				X	
*Only if the dose of diabetes medications has been changed after enrollment												

WEEK	- 6	-4	-1	0	4	8	12	16	20	23	24	28
VISIT	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
TEST												
CK-18				X							X	
Genotyping (SNPs of interest)				X								
Inpatient metabolic testing												
Insulin sensitivity study				X							X	
Rates of novo lipogenesis (DNL) and gluconeogenesis				X							X	
Indirect calorimetry				X							X	
Urine collection for metabolic measurements				X							X	

6.4.3 Vital Signs

Vital signs will be assessed at each visit including the screening visit and from V1 to V4. Please refer to section 5.2.5 for the detailed technical procedure. For methods and normal values definition, see Appendix B: Methods and Normal Values for Vital Signs, Waist and ECG.

6.4.4 Electrocardiogram

Please refer to Appendix B: Methods and Normal Values for Vital Signs, Waist and ECG for the detailed technical procedure.

6.5 Data Safety Monitoring Committee

Below is the list of members of the DSMB for the lanifibranor clinical trial. They will meet on a quarterly basis and monitor for protocol deviations, adverse events and review any serious adverse events.

Chair:

Steve Anton, Ph.D.
Associate Professor & Clinical Research Division Chief
Department of Aging and Geriatric Research
Department of Clinical and Health Psychology
College of Public Health and Health Professions
College of Medicine, University of Florida
Gainesville, FL 32611
Phone: 352-273-7514
Fax: 352-273-5920

Members:

Roberto J. Firpi, M.D., M.S., AGAF, FAASLD, FACG
Associate Professor of Medicine
University of Florida
Section of Hepatobiliary Diseases and Transplantation

Department of Medicine
1600 SW Archer Rd, MSB Room M440
Gainesville, FL, USA
Phone: 352-273-9466

Maryam Sattari, M.D.
Clinical Associate Professor of Medicine
University of Florida
Department of Medicine, Division of Internal Medicine
1600 SW Archer Rd
Gainesville, FL, USA
Phone: (352) 265-0140

Juan Manuel Muñoz Pena
Assistant Clinical Professor
Division of Endocrinology, Diabetes and Metabolism
Department of Medicine
1600 SW Archer Rd
Gainesville, FL, USA
Phone: (352) 273-8656

Margaret C. Lo, MD FACP
Associate Professor of Medicine
Associate Program Director, UF Medicine Residency Program
Program Co-Director, VA Chief Residency in Quality Safety
Director, UF Primary Care Track
Department of Medicine, Division of Internal Medicine
University of Florida College of Medicine
Gainesville, FL 32610
(352) 265-0651 (office)
(352) 265-0239 (residency office)
(352) 265-0153 (fax)

Verification according to University of Florida standards for clinical trials.

All data must be verifiable in source documentation other than the eCRF.

7 Data Quality Assurance

7.1 Monitoring

The PI and Medical staff will verify during monitoring visits, the monitors will verify the adherence to the protocol, the maintenance of all study-related records and the accuracy and

completeness of all eCRF entries compared with source data in order to ensure that:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol, ICH-GCP and all applicable regulatory requirements

Any discrepancies identified must be resolved. The monitors will review source documents to confirm that the data recorded on eCRF is accurate. The investigator and institution appropriate regulatory authorities' direct access to source documents to perform the verification according to University of Florida standards for clinical trials. All data must be verifiable in source documentation other than the eCRF.

The study sites may be subject to review by the Institutional Review Board (IRB)/Data Safety and Monitoring Board (DSMB), and/or to quality assurance audits, and/or to inspection by appropriate regulatory authorities. The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

7.2 Data Recording

Electronic Data Capture (EDC) will be used for this study, meaning that all data will be entered on an eCRF at the investigational site. This eCRF will be specifically designed for the study. We will use a program called REDCap™ (Research Electronic Data Capture; https://www.ctsi.ufl.edu/research/study-design-and-analysis/redcap). It is a secure, Web-based application designed to support traditional case report form data capture for research studies performed at NIH-based Clinical Translational Science Institutes (CTSIs) use. It is a flexible platform that allows Export data to Microsoft Excel and statistical packages for easy data analysis.

This database platform has several practical advantages:

- HIPAA Compliant
- Data is stored on a secure server
- Database access requires user authentication with password
- Data access based on an individual's role on a project
- Logging and audit trails on all data interactions
- IRB and UF Privacy Office approved for collection and storage of PHI (private health information).

The University of Florida (UF) requires that all data collected or stored in REDCap follow the following processes and procedures:

- All human research studies must have Institutional Review Board (IRB) approval before the research study can be moved to production and data collection can commence.
- The name of the Principal Investigator (PI) must be provided.
- If the research study will include other collaborative personnel such as co-investigators, technicians and students, the principal investigator must assure that the personnel are listed on the approved IRB form.
- If data is collected that is considered either sensitive, protected health information, or HIPAA information, then prior to using the system the user must complete all necessary

training including but not limited to require HIPAA training.

- Social Security Number training is required annually for all UF personnel who use SSNs in their work or research. The “Protecting Social Security Numbers” training module is available only through myTraining. http://mytraining.hr.ufl.edu.
- It is the responsibility of the principal investigator to ensure that collaborative personnel have the appropriate study-specific and related training and have reviewed the required safeguards according to UF policies and procedures.
- Users of REDCap™ must adhere to all UF computer policies, regulations, rules and standards. It is the responsibility of the principal investigator and the administrator of each account to routinely monitor their REDCap projects.

REDCap Support and Contingency Policies

The Clinical and Translational Science Institute (CTSI) at the University of Florida provides the use of REDCap™ (Research Electronic Data Capture) software as a service for UF investigators and their teams to collect study data. This service includes the REDCap application software hosted in a web server, server space for data storage, regular system backups, software patches and upgrades. In the event of a system shut-down, a 24 hour recovery time objective is achievable. UF Health IT has a Disaster Avoidance and Recovery Plan that covers responsibilities, communication, and escalation. The recovery point objective for the REDCap database is 1 hour (no more than 1 hour of data loss). The recovery point objective for the web server is 24 hours (no more than 24 hours of data loss).

• PIs will maintain printed copies of REDCap forms to enable offline data collection and subsequent data entry if there is a need to collect data during an outage. In the event of an expected catastrophic disaster, such as loss of a data center due to a hurricane, the REDCap Support Team (Administrators) will notify all REDCap users via e-mail of the potential threat.

• PI’s are advised to move/export data to a disk and to a storage area approved for sensitive data. In the event of scheduled System maintenance, the REDCap Support Team (Administrators) will notify all REDCap users via e-mail one week prior, one day before and on the day of the scheduled maintenance. All users are notified via e-mail when the system is available again. Data is not available for export from REDCap during a REDCap outage.

In this clinical trial, only anonymized data will be recorded based on the clinical data collected. The anonymized data of medical information includes the results of the trials tests and will be communicated to the Principal Investigator or its representative.

Only members of the research team, who also form part of the patient's direct clinical care team, at the participating sites will have access to patient records as part of their medical care and will use these records to screen for potentially eligible patients. Patients who consent to enter the trial are informed that staff from the research team, the Principal Investigator (and its representatives), relevant regulatory authorities and ethical committees may require access to their full medical records for monitoring and auditing purposes.

Database and results of statistical analyses, narratives of SAEs will be transmitted to Inventiva SA which will contract out study report writing.

The clinical study report will be reviewed and signed by the Principal Investigator.

The study (validation of the final report), the data will be totally anonymized and will be stored on a dedicated and secured slot at the Principal Investigator site.

Only authorized Principal Investigator employees or its representative will have access to the data.

7.3 Data Management

7.3.1 Responsibilities

The PI will designate the Data Managers who will be provided with all tools, instructions, and training necessary to complete the eCRF into REDCap, and each user will be issued a unique username and password.

The Data Management will be responsible for data processing, in accordance with REDCap data management procedures. Data will be managed by the PI (Dr. Cusi) and his research team, who will be responsible for data processing, quality control, storage, monitoring, and analysis. Data will be also shared with Inventiva for additional analysis and result publication. Only de-identified datasets from which all PHI has been removed will be shared with Inventiva.

The Principal Investigator, together with his designated medical staff, will verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable, or unknown, the Investigators will have to indicate this in the eCRF. The Investigators will be required to electronically sign off the clinical data.

The Monitors will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies.

All entries, corrections, and alterations will be made by the Investigator or his/her delegate. The Monitors will not enter data in the eCRFs.

7.3.2 Data Collection and Validation

All clinical, laboratory and imaging data will be entered into the eCRF at the investigational site. This will be done for each patient (screen failure and enrolled), by the Investigator or designee, and signed by the Investigator. A hard copy of the clinical data will be kept in locked cabinets and locked offices at our CTSI (second floor, diabetes research section), strictly following current UF IRB privacy guidelines of confidentiality at all times.

A unique subject code will identify the subjects on the eCRF. Each participant will be assigned a unique study identification number. A link to the study identification number will be stored separately. Data will be collected on case report forms or source documents. Data quality control will be monitored regularly along with real-time programmed data checks.

Once clinical data of the eCRF have been entered into REDCap, corrections to the data fields will be audit trailed, meaning that the reason for change and the name of the person who performed the change, together with time and date, will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF in REDCap will be determined in advance and documented on the “delegation form”.

Automatic checks and listings will be designed and performed according to the data validation plan, developed by Data Managers. In case of missing values, out of range values, data inconsistencies or values that fail logical checks, queries will be edited in the EDC application. In addition, the Monitors and Data Manager(s) can raise manual queries in the EDC application.

The appropriate investigational staff will answer automatic and manual queries. This will be audit-trailed by the EDC application, meaning that the name of the person who answered and the time and date stamp are captured.

7.3.3 Data Coding

AEs and Medical History (MH) will be coded using the last version of MedDRA terminology. Concomitant medications will be coded using WHO Drug 2016 Q1 (or a more recent version) terminology.

The medical coding will be performed by the Data Manager coding specialist and reviewed by a Principal Investigator before being submitted to Inventiva for approval.

7.3.4 Database Lock

Once validated, the database will be locked so that no more change will be possible on the frozen data.

After database lock, the Principal Investigator will receive a CD-ROM of the patient data (eCRF data + audit trail) for archiving at the investigational site.

7.3.5 Database Transfer

Final validated data will be transferred in a secure way to the Inventiva Biostatistical team in Excel or the format that best meets the Inventiva Biostatistical team after mutual agreement.

7.4 Independent Audit

The Principal Investigator will permit an independent audit by an auditor mandated by Inventiva S.A., after reasonable notice. An audit or a regulatory inspection is intended to determine if the study was conducted as per protocol (PP), GCP and applicable regulatory requirements, if the rights and well-being of the patients were protected, and if the data relevant for the evaluation of the IMP were captured, processed and reported in compliance with the planned arrangements.

7.5 Regulatory Inspection

Regulatory authorities may perform an inspection of the study including several years after its completion. As for an audit, the investigator will permit a direct access to all study documents, drug accountability records, source records and source data. If an inspection is announced, Inventiva S.A. will be informed without delay.

8 Statistical Methods

Studied population:

Modified ITT and safety population: All randomized patients who took at least one dose

Evaluable patients: Patients belonging to the mITT with at least one pre-randomization and one post-randomization assessment of IHTG.

8.1 Efficacy Assessments

Primary outcome and Primary efficacy criterion: IHTG quantified by ^{1}H-MRS.

Primary outcome: Change from baseline to week 24 in IHTG quantified by ^{1}H-MRS.

Primary measure of the magnitude of treatment effect: difference between lanifibranor and placebo in the mean change from baseline to week 24 of IHTG.

Threshold of clinical pertinence of the effect size: an absolute difference between treatments of 3% in the mean change from baseline to week 24 is probably at the limit of clinical pertinence. This represents a mean decrease in IHTG of 20% in lanifibranor group and 0% in placebo group. Considering a standard deviation of 7 this is a standardized effect size of a little less than 0.43 which is in the lower-medium class (between 0.4 and 0.5) of treatment effect. Therefore, an absolute reduction of 3.5% (relative reduction of 23.3%), leading to a standardized effect size of 1.5 (medium effect size), is considered clinically pertinent. Indeed, assuming the normality of the distribution of the change from baseline, a mean absolute reduction of 3.5% in IHTG for the tested drug and 0 for placebo, a baseline at 15%, a standard deviation of 7% and a resolution of NAFLD

from 5.5% and below, the expected percentage of patients with A IHTG of 5.5 or less ("resolution" of NAFLD) is 19.5% with the tested drug and 8.7% for the placebo corresponding to a 2.24 times more chance of observing a resolution in the tested drug than in the placebo group.

Using the expected treatment effect in the sample size calculation (35% relative reduction in IHTG for the tested drug and 0% for placebo), then the expected absolute effect size is 5.5%, the standardized effect size is 0.79 that is very close to a large magnitude (0.8) of treatment effect. The expected percentages of "resolution" of NAFLD under the assumption of normality of the change from baseline is 28.4% versus 8.7% corresponding to 3.26 times more chance to get an observed resolution of NAFLD for lanifibranor compared to placebo.

Secondary endpoints: The following changes from baseline to 24 weeks of treatment will be evaluated and used as secondary endpoint:

- Proportion of "responders" defined as the percentage of patients reaching a decrease from baseline in IHTG (quantified by ^{1}H-MRS) of ≥ 30% at 24 weeks. The definition of "responders" as those with a ≥ 30% reduction in liver fat by ^{1}H-MRS is empiric as there are no studies (except the Belfort et al, NEJM 2006 (1) and Cusi et al (2) with pioglitazone) comparing simultaneously ^{1}H-MRS with liver histology, but this threshold is likely to correlate with positive histological changes in NASH, based on investigator's experience.
- Proportion of patients considered as having resolution of NAFLD (≤5.5% IHTG quantified by 1H- MRS) at 24 weeks (highly likely to translate into histological benefit in NASH).
- Changes in hepatic fibrosis by several techniques (one or all may be used):

a) vibration-controlled transient elastography (Fibroscan) (3);

b) two-dimensional magnetic resonance elastography (2D-MRE) (4); and

c) T1 MRI mapping scanning protocol that allows for the accurate non-invasive measurement of liver fibrosis (5).

- Change in plasma biomarkers of liver fibrosis (i.e., cytokeratin CK-18, proC3.
- Change in metabolic outcomes standard for such pilot trials (see our work in ref. 1,2,6 at week 24 of treatment, and will include:
    - Determination of glucose tolerance/insulin, hepatic insulin sensitivity, gluconeogenesis, de novo lipogenesis (DNL).
    - Oral glucose tolerance test.
    - Glycemic control: HbA1c, advanced lipid testing.
    - Biomarkers of adipose tissue metabolism (i.e., plasma adiponectin and adipokine panels measured multiplex platform).
- DNA testing to assess SNPs related to NAFLD (PNPLA3, TM6SF2, others) (36).
- Safety and tolerability assessments as standard for clinical treatment trials (vital signs, electrocardiograms, hypoglycemia, laboratory parameters such as elevation in liver or pancreatic enzymes, other).

8.2 Sample Size

Based on the most recent studies patients with NAFLD are expected to have a baseline IHTG of approximately 15%. The earlier power calculations based on results with pioglitazone from a 6-month study (1) and a more recent 18 month RCT (2) but they were revised in the protocol based on the recent results with lanifibranor 800 mg/day (same dose as this study), a 6-month RCT (NATIVE) that used liver biopsy (histology) as the primary endpoint (provided in detail by Inventiva to the PI Dr. Cusi). In NATIVE, the proportion of patients with a reduction in steatosis

to lanifibranor was 73% versus 26% with placebo; greater than with pioglitazone in the 6-month Belfort et al study [1]). Based on these most recent results, this would translate to liver fat imaging on ^{1}H-MRS of a relative reduction of fat liver with lanifibranor to be ≥50% compared to placebo. This represents a change of ≥7.0% with lanifibranor versus the control group. The expected standard deviation of the change from baseline is expected to be 7%. Considering a type I error of 0.05 (2-sided), a power of 0.80, an allocation ratio of 1:1, the same variance in both treatment groups and a parametric test of mean comparison, the required sample size per group is 15 patients to complete treatment. Assuming that 10 % of randomized patients will not complete the trial, the total number of patients to be randomized is 33-34 patients. Considering a type I error of 0.05 (2-sided), a power of 0.80, an allocation ratio of 1:1, the same variance in both treatment groups and a parametric test of mean comparison the required sample size per group is 15 patients. Assuming that 10 % of randomized patients will not complete the trial, the total number of patients to be randomized is 34.

8.3 Randomization

Patients will be randomized equally 1:1: to either dose of lanifibranor or placebo.

The randomization list will be setup with blocs of size equal to 4.

8.4 Protocol Deviations

Protocol deviators will be identified and classified at the blind review. Only patients with major deviations will be discussed in the Clinical Study Report and excluded from the per protocol analysis.

8.5 Data sets Analyzed

- **Full analysis set (FAS)**

The full analysis set consists of all randomized patients who received at least one dose of the assigned treatment. In case of error in the assignment of treatment, the actual treatment will be used in the FAS instead of the treatment assigned in the randomization list. This set is the primary set of patients used in the primary analysis of the primary efficacy endpoint. It corresponds more or less to efficiency evaluation of treatment.

- **Randomized set of patients**

The randomized set of patients consists of all randomized patients. In case of treatment error, the treatment assigned in the randomization list will prevail over the actual received treatment. In case of no post-randomization efficacy assessment the patient will be a failure (see handling of missing data). This set of patients will be used in a sensitivity analysis.

- **Set of evaluable patients**

The set of evaluable patients will consist of the FAS after exclusion of all patients who did not have an efficacy evaluation (IHTG) at week 24. Patients did not necessarily took their treatment up to week 24. In case of error in the assignment of treatment, the actual treatment will be used in the FAS instead of the treatment assigned in the randomization list.

- **Per protocol set of completers**

This set is composed of all patients who completed the treatment and the study and who were free from major protocol deviation that can bias the estimation of the treatment effect at week 24. Patients with major deviations will be listed during the blind review and the reason for exclusion will be provided. In case of treatment error, the patient will be assigned to the group corresponding to the actual treatment received. This set will be used in efficacy evaluation for estimating and testing the treatment effect in the best situation (squeaky clean analysis) *i.e.* treatment completers,

assessment at 24 weeks for all patients, no major protocol violations

- **Safety set of patients**

The safety set of patients will include all patients who have taken at least one dose of treatment (IVA 337 or placebo), regardless any protocol deviations. In case of treatment error, the actual treatment will be used. Safety analyses will be conducted on the safety population

8.6 Demographic and Other Baseline Characteristics

8.6.1 Patient Demographic Characteristics, Medical History and Diagnoses

Safety characteristics, including demography, medical history, entrance criteria deviations will be summarized using the descriptive statistics (N, mean, standard deviation, median minimum and maximum for quantitative values and counts and percentages for qualitative variables).

8.6.2 Previous Medications

The use of prior medications will be summarized.

8.6.3 Patient history

Medical history of patients will be provided

8.7 Safety Analysis

The review of safety and tolerance will be performed on the safety population. The safety analysis will be based on the reported AEs and other safety information. The Principal Investigator will use its most updated list of potentially clinically significant abnormalities (PCSA) in clinical laboratory tests, vital signs, and ECG for the final analysis. The effect of the demographic differences (gender, age, etc.) and risk factors of clinical relevance will be explored in case of any potential concern.

8.7.1 Extent of Exposure

The extent of exposure will be summarized descriptively (N, mean, median, standard deviation and range) using treatment exposure duration. Treatment exposure duration (in days) is defined as: (Date of last dose of study product - First intake of study product date). In case of treatment interruption, the actual duration of treatment will be used. The distribution and cumulative distribution of patients by treatment exposure duration will be presented graphically for the safety population.

8.7.2 Adverse Events

Each AE will be associated to a "preferred term" and classified by "system-organ class" according to the latest MedDRA. The AE parameter of interest is the number and percentage of patients experiencing: - at least one event - an event under each recorded preferred term, and an event under each recorded system-organ class. These frequencies apply to all AEs, regardless of relationship of the event to lanifibranor.

- **Definitions:**

Adverse events will be coded according to Medical Dictionary for Regulatory Affairs (MedDRA) and coded as treatment emergent (TEAE) / non-treatment emergent (non-TEAE) according to the following definitions. TEAEs are defined as events occurring on or after the day of first dose intake of study product and up to follow up visit. Additionally, events present before the first dose of study product, but worsening under treatment are considered as TEAEs. Although every effort will

be made to establish the onset date and time, events with missing onset date will be considered as TEAEs. An AE that will not qualify as a TEAE will be considered as a Non-TEAE. Non-TEAES will be summarized separately from TEAES and will be presented in the same manner as TEAEs.

- **Treatment Emergent Adverse Events**

A given TEAE will be counted once only per patient. The percentages will be calculated in relation to the population exposed (i.e., safety population). All TEAES will be analyzed, irrespective of their causal relationship with allocated treatment. Summary tables will be provided, showing the following:

- count of exposed patients,
- count and percentage of patients with at least one TEAE,
- count and percentage of each TEAE: TEAEs will be sorted by decreasing order of organ system frequency then by decreasing order of preferred term frequency,
- count and percentage of each TEAE, not taking into account organ system.

In addition, TEAEs will be described according to their time to onset with same categories as for duration of exposure, their maximal intensity and their relationship to gender and age of patient, time from first intake, outcome, seriousness criteria, corrective treatment, duration, treatment received, and action taken. Patient data listings will be provided for all AEs, TEAEs, AEs leading to study discontinuations and SAEs.

Deaths and Serious Adverse Events Incidence of SAEs (irrespective of their emergence classification and relationship to lanifibranor) and deaths will be listed and summarized.

- **Adverse Events leading to treatment discontinuation**

Adverse event leading to discontinuation of the study will be tabulated, irrespective of their emergence classification and irrespective of their relationship to lanifibranor.

8.7.3 Other Observations Related to Safety

- **Laboratory tests**

The analysis will focus on potentially clinically significant abnormal (PCSA) values which will be defined in the Statistic Analysis Plan (SAP). The incidence of PCSAs will be summarized for each clinical laboratory test. The summaries will include patients exposed to study medication who have at least one laboratory test performed after the first study product intake and, when required by the definition of the abnormality, with an available baseline value and available normal ranges. For these descriptions, the baseline value will be the latest available measure before the first study product dose intake. International units will be used in all listings, tables and graphs. Results and changes from baseline of laboratory parameters will be summarized by mean, standard deviation, median, minimum and maximum at each time point and for the final on-treatment visit. Unscheduled and/or repeated results will only be listed and not summarized.

Shift tables and other tabular and graphical methods will be used to present the results for tests of interest. Listings will be provided with flags indicating clinically significant out-of-range values, clinically non-significant out-of-range values as well as the PCSA values.

- **Vital signs and ECG**

Descriptive statistics by time point will be computed on actual values and changes from baseline for vital signs and ECG data. The baseline value is defined as the last measure before study product intake. ECG parameters collected are heart rate, PR interval, QRS interval, QT, QTcB (Bazett) intervals. Descriptive statistics (means, standard deviations, and ranges) and changes from baseline values for all visits will be provided. Patients with PCSA for each vital sign or ECG data parameter

will be identified and listed. The incidence of PCSA at any time point will be summarized for each vital sign parameter. The summaries will include patients who have at least one measurement performed after the first study product intake. When the PCSA definition involves a change from the baseline value, patients also need to have a baseline value to be included in the summaries. Results and changes from baseline of the following vital sign parameters will be summarized by mean, standard deviation, median, minimum and maximum at each time point and the final on-treatment visit:

- Heart rate: supine,
- Systolic blood pressure: supine,
- Diastolic blood pressure: supine,
- Weight.

Shift tables and other tabular and graphical methods (plots of mean over time) may be used to present the results for parameters of interest.

Confirmatory-inferential analysis may be done for parameters of interest. Listings will be provided with flags indicating clinically significant out-of-range values, clinically non-significant out-of-range values as well as the PCSA values.

- **Physical examination**

For physical examination anomalies will be listed and frequencies tables will be computed.

8.7.4 Efficacy Analyses

Primary efficacy analysis

The primary population will be the modified intent to treat FAS population composed of all randomized subject who received at least one dose and had at least one post-randomization efficacy assessment.

The primary outcome will be the change from baseline to week 24 in IHTG.

The primary model will be a general linear model using the change from baseline to week 24 as the response, the treatment as covariate as well as the baseline of IHTG. Few covariates can be added in the SAP to take into account known confounding factors.

The magnitude of the treatment effect will be the between treatment group difference in the mean change from baseline to week 24 in IHTG adjusted for baseline of IHTG.

The primary rule for handling the IHTG missing data at Week 24 is the use of the baseline at Week 24 in case the mean change from baseline in placebo group is equal to zero or is an improvement or if the reason for missing data is definitely not related to treatment or disease progression. If the relative change from baseline to week 24 in the placebo group is a deterioration of IHTG then the relative deterioration observed in the placebo group will be applied to all missing IHTG at week 24 that are possibly related to treatment or disease progression.

Sensitivity analyses

The primary analysis of the primary efficacy assessment will be performed after the following modification.

- Use of the randomized set of patients.
- Use of the evaluable set of patients
- Use of the per protocol set of patients

- Use of a non-parametric test (Mann and Whitney) especially in case of outliers or if the distribution of change from baseline is quite skewed. Hodge Lehmann estimator will be used to estimate the magnitude of treatment effect.
- Use of the Q3 (third quartile) estimate of the relative change from baseline to week 24 of the placebo distribution (from the most improved to the most worsened) for imputing missing IHTG at week 24.

Secondary efficacy analyses of the primary efficacy assessment

The following proportions will be estimated per treatment group with the Clopper Pearson 95% CI and compared with a Fisher exact test in the FAS, the evaluable set of patients and per protocol set of patients:

- Proportion of "responders" defined as the percentage of patients reaching a decrease from baseline in IHTG (quantified by ^{1}H-MRS) ≥ 30% at 24 weeks. In case of missing outcome at weeks 24 the patient is a non-responder.
- Proportion of patients considered as having resolution of NAFLD (≤ 5.5% IHTG quantified by ^{1}H- MRS) at 24 weeks.

Other secondary analyses

- Between treatment difference in the change from baseline to week 24 in hepatic fibrosis will be estimated and tested with a general linear model for each technique used:
  a) Vibration-controlled transient elastography (Fibroscan);
  b) two-dimensional magnetic resonance elastography (2D-MRE); and
  c) T1 MRI mapping.

  The general statistical approach will be similar to the primary analysis and subordinated analyses.

- Between treatment difference in the change from baseline to week 24 in each plasma biomarkers of liver fibrosis (cytokeratin CK-18, proC3) will be estimated and tested using the same approach as the primary analysis.

- Between treatment difference in the change from baseline to week 24 in metabolic outcomes will also be estimated and tested for:
  - Hepatic insulin sensitivity, gluconeogenesis and de novo lipogenesis (DNL).
  - Oral glucose tolerance test.
  - Glycemic control: HbA1c, advanced lipid testing.
  - Biomarkers of adipose tissue metabolism (i.e., plasma adiponectin and adipokine panels measured by the gold-standard Millipore multiplex platform).
- The percentage of patients achieving an improvement in HbA1c or plasma lipid targets will be analyzed using a logistic regression model with treatment and baseline HbA1c and lipid profile as covariates, respectively.
- The time course of repeated measures of FPG, HbA1c, lipid parameters, and others will be estimated and tested using mixed models for repeated measures to account for the correlation amongst measures after careful selection of the proper covariance structure.
- Hypoglycaemia rate will be fitted to a negative binomial model to test the treatment effect.
- The percentage of patients having a hypoglycaemia reported or not as AE will be

analyzed using a loglikelihood test, unless there are too few events in which case a Fisher exact test will be used.

- DNA testing to assess SNPs related to NAFLD (PNPLA3, TM6SF2, others).
- Immunohistochemistry: change in the semi-quantitative score of ballooning and stellate cell activation from baseline to end of treatment (week 24) will be compared using a Wilcoxon Mann Whitney test.

Planned exploratory analyses:

The SAP will provide more details on the presented analyses as well as on other exploratory criteria such as quality of life assessment.

All secondary efficacy analyses will be performed using a mixed model for repeated measures or an ANCOVA model if only one post-randomization measure is available. CMH test stratified on diabetes will be used for qualitative variables.

Exploratory analyses on the biomarkers measurements and other evaluations will be proposed and described in the statistical analysis plan.

The final version of the Statistical Analysis Plan will be issued before freezing of the database the break of the randomization code. Any clarification brought in the SAP concerning handling of data and statistical analyses will prevail over any other interpretations of the protocol unless it is the source of major inconsistencies.

9 Patient Withdrawal & Replacement & Clinical Trial Stopping Rules

9.1 Patient Withdrawal

Participation in the study is strictly voluntary. The patients have the right to withdraw from the study at any time for any reason, 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 must be avoided.

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

- 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.
- Major protocol deviation: e.g. lack of compliance with scheduled visits, non-compliance with study treatment, treatment with prohibited medication during the study (see section 4.3.3)
- Any deterioration in cardiac status
- CTCAE grade 3 or higher possibly or probably related to study drug OR CTCAE grade 4 or higher regardless of attribution to study drug
- Additional individual discontinuation should be based on known toxicities and side effects of the drug and its class, specifically for metabolic, renal, hematologic, and hepatic toxicity. If any of the following criteria are met, the patient should be immediately discontinued from drug and followed until resolution of adverse events and laboratory values have

returned to baseline.

1. Total Bilirubin ≥ 3.0 md/DL
2. Total CPK > 5X ULN
3. Lipase level increase above inclusion criteria (i.e., lipase above 1.3X ULN **if not on a DPP-IV inhibitor,** or >2.0X ULN if on a DPP-IV inhibitor) and re-confirmed on testing within 7 days; or lipase > ULN in any patient with symptoms compatible with pancreatitis; or in asymptomatic patient with lipase above inclusion criteria and when retested (without drug interruption) remains above inclusion criteria within 7 days.
4. eGFR with a decrease of more than 20% below the lower limit of inclusion criteria (or < 48 ml/min/1.73 m^2) and where the value is reconfirmed after 24 - 48 hours repeat. Additionally, any subject who requires renal replacement therapy should also be discontinued from drug.
5. Hemoglobin < 10 mg/dL or HCT < 30%
6. Platelets < 100,000 per microliter of blood
7. WBC < 2.5 x 10^9/L and /or ANC <1.5 K/µL
8. Regarding hepatic toxicity
    - For BLM < 2x ULN, for ALT or AST >5x BLM
    - For BLM ≥2X ULN but < 5X ULN, for ALT or AST > 3X BLM
    - For BLM ≥ 5X ULN, for ALT or AST > 2X BLM
    - For ALT or AST increase > 2X BLM accompanied by a concomitant total bilirubin increase to > 2X BLM OR an INR increase by > 0.2

    For elevations of liver enzymes accompanied by symptoms consistent with hepatic injury [e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)]http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

- Investigator's decision for any other reason

If a patient discontinues the study, the investigator will make reasonable efforts to obtain the reason and to perform all protocol-defined end of study assessments as soon as possible. The reason and circumstances for premature discontinuation (e.g. consent withdrawal, AE, lost to follow up, etc.), 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 6.2.2), the patient will be followed until outcome, i.e. 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 their 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.

9.2 Study Stopping Rules

In addition, the trial will be stopped if:

1. Three patients develop the same Grade 3 CTCAE
2. OR two patients develop any Grade 4 CTCAE
3. OR one patient develops a Grade 5 CTCAE

9.3 Unblinding Process

9.3.1 Unblinding for emergency

The code breaks sealed envelopes will be provided and will be kept by the Principal Investigator.

The Principal Investigator is responsible for ensuring appropriately trained staff members are available to open code breaks sealed envelopes when required for medical emergencies which may be required out of normal working hours.

Sealed envelopes containing the code-break information will be provided to the Pharmacovigilance and safety Institution (Stragen, see section 2.3).

Details of any emergency unblinding shall be documented fully in the Investigator's file and research pharmacy file(s). This includes, but may not be limited to:

1) Date,
2) Subject details,
3) Reason for unblinding,
4) The results,
5) Name and role of the individual requesting the unblinding,
6) Name and role of the individual carrying out the unblinding.

If the clinical trial research pharmacy or an individual as named on the Delegation Log has performed the procedure, they will inform the Principal Investigator, the trial identifier, subject number and name and title of the person making the request, but NOT the result. The details shall be included in the statistical report.

9.3.2 Unblinding for DSMB

The Principal Investigator will create a University of Florida Data Safety and Monitoring Board (DSMB) to ensure safety surveillance during the study. This safety committee may recommend unblinding of any data for further analysis is deemed necessary for the safety of the subjects. If so, the Principal Investigator will be notified, and an independent ad hoc group will be created in order to maintain the blinding of the study and of the participating personnel.

9.3.3 Unblinding at End of Trial

The Statistical Analysis Plan shall be provided in the protocol or be finalized prior to the release of the randomization codes. Changes to the statistical analysis plan shall be version controlled. A record shall be kept in the Investigator TMF to confirm when the randomization code was requested and when provided.

10 Training & Information

10.1 Training

All persons involved in the study will be trained in an effort to standardize relevant methods, ratings and data capture and to prevent deviations.

10.2 Information of the Investigator

The investigator will receive all the relevant information for a safe use of the IMP as the study proceeds.

11 Records & Data

11.1 Source Records & Data

Source data are all the information in original records and certified copies of original records of clinical findings, observations, or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audits, IEC reviews and regulatory inspections, with a direct access to all the required source records. For each patient enrolled, the investigator will note in the source records that the patient participates in this study, and will record the following information: concomitant therapies, clinically significant adverse events and a statement at patient end of participation.

11.2 Case Report Forms

Electronic Case Report Form (eCRF) will be provided by the research team. The investigator is responsible for maintaining adequate and accurate data into the eCRF which has been designed to record all observations and other data pertinent to the clinical investigation.

All data requested on the eCRF must be filled out completely by the investigator or the investigator team. All data captured for the study is planned to be electronic. The eCRF should be reviewed and electronically approved by the investigator.

All missing data must be explained. If any entry error has been made, to correct such an error, enter the correct data above it. All such changes will be must electronically signed with the reason for the correction if necessary, by an authorized (investigator/co-worker) person.

eCRF and all other source data must be easily accessible for review during the programmed monitoring visits. Once the clinical monitor has verified the contents of the completed eCRF against the source data, the system will be verified electronically by the clinical monitor for those pages. Queries may be raised if the data are unclear or contradictory, which must be addressed by the investigator.

Patients are not to be identified in the eCRF by name or initials and birth date. Appropriate coded identification, e.g. patient number in combination with year of birth must be used.

12 Confidentiality

12.1 Confidentiality of Patient Data

The Principal investigator will ensure that the confidentiality of the patients' data is preserved. On eCRFs or any other documents for the patients will not be identified by their names, but by a study code. Documents not for transmission e.g. the confidential PHI and the signed informed consent forms will be maintained by the investigator in strict confidence.

These data will be collected and processed with full precautions to ensure confidentiality and compliance with applicable UF IRB data privacy protection laws and regulations. Technical and organizational measures will be in place to fully protect PHI against unauthorized disclosures or

access, accidental or unlawful destruction, or accidental loss or alterations. Any personnel with access to personal data must agree to keep the identity of subjects strictly confidential.

The informed consent that will be obtained from all participants includes explicit consent to access and process PHI and for the investigator/institution to allow direct access to the original medical records (source data/documents) for study-related monitoring, audit, IRB review, and regulatory inspection. This consent also addresses the transfer of de-identified datasets to be shared with to other countries (e.g., Inventiva headquarters) or other authorized entities (e.g., FDA).

The participant retains the right to request through the PI access to their personal data and rectification of any data considered to be incorrect or incomplete. Reasonable steps will be taken to respond to these requests, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

12.2 Confidentiality of Data

Any information on the IMP, this study and its results is confidential information. The investigator, study site personnel and IEC members will not use, publish, or otherwise disclose any confidential information without the prior written authorization from Inventiva S.A. Any data, results, inventions and patents that may arise from this study will be the exclusive property of Inventiva S.A.

13 Reporting & Publication

13.1 Study Report

All the relevant data and information will be reported in a study report prepared by a CRO and submitted to the investigators for review comments and signature. The final study report will be used for the further development of the IMP and regulatory submissions.

13.2 Disclosure of Data and Publications

No information provided by Inventiva SA 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 Inventiva SA.

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.

After regulatory clearance, the study will be registered by the Principal Investigator in the ClinTrials.gov database. The Principal Investigator 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 Inventiva SA at least 1 month prior to (i) submission of such written materials for publication, or (ii) any proposed oral disclosure to a third party. Inventiva SA shall have the right to comment on such written material/outline and to take any necessary action to protect its intellectual property; the Principal Investigator, in determining the final form of disclosure, shall consider such comments in good faith. Notwithstanding any of the above, the Principal Investigator 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 Inventiva SA with complete test results and all data derived from the study in accordance with the protocol.

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

14 Record Keeping

14.1 Study Site Records

The Principal Investigator is responsible for maintaining all the records which enable the conduct of the study at the study site to be fully understood. The study documentation and source records will be archived for the maximum period of time permitted by local requirements. The Principal Investigator will complete the confidential patient identification list which provides the sole link between source records and anonymous eCRF data. The Principal Investigator will retain this confidential list and the signed consent forms for at least fifteen years after the completion or discontinuation of the study. No study site records may be destroyed without prior written agreement between the Principal Investigator and Inventiva S.A. If the Principal Investigator intends to assign the study documents to another party, or to move them to another location, Inventiva S.A. must be notified.

14.2 Study Master File

The Principal Investigator will archive the study master file in accordance with GCP and applicable regulatory requirements.

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16 APPENDICES

16.1 Appendix A: World Medical Association Declaration of Helsinki

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

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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

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

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

General Principles

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

1/8

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks, Burdens and Benefits

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

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

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

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

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

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

Vulnerable Groups and Individuals

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

All vulnerable groups and individuals should receive specifically considered protection.

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

Scientific Requirements and Research Protocols

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

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

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

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

Research Ethics Committees

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

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

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

Privacy and Confidentiality

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

Informed Consent

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

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

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

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

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

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

Use of Placebo

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

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

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

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

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

Post-Trial Provisions

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

Research Registration and Publication and Dissemination of Results

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

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

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

Unproven Interventions in Clinical Practice

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

16.2 Appendix B: Methods and Normal Values for Vital Signs, Waist and ECG

1. VITAL SIGNS

Systolic and diastolic blood pressure, and heart rate measures are performed by a sphygmomanometer, using the oscillometric method lying after 10 minutes rest (DBP: $50 \geq N \geq 90$ mm Hg; SBP: $100 \geq N \geq 140$ mm Hg; HR: $50 \leq N \leq 100$ bpm). To be measured at all visits.

2. WAIST MEASUREMENT

The Waist measurement must be done at midway between the top of the hip bone and the bottom of the ribs during a normal breathe out. To be done at all visits.

3. ELECTROCARDIOGRAM RECORDINGS

A 12-lead standard ECG to be performed at V1 (screen) and at V11 (24 weeks).

16.3 Appendix C: Procedure for Preparation of (6,6-D2)-Glucose Infusates

Preparation of 2D-glucose infusates

Date:

Subject:

Operator:

(6,6-2D)-glucose (0.50 gm/ml)

Catalog No.:
Lot No.
Date prepared:

0.9% NaCl

Catalog No.:
Lot No.:

D20 glucose

Catalog No.:
Lot No.:

NOTE: If there are changes in this process during the course of the clinical study, written notification will be provided to the Sponsor and the Investigator, and a protocol amendment will not be required. The most current version of Standard Operating Procedure for this process is maintained at the investigator site.

I. Baseline infusion

Materials: 0.9% NaCl for infusion
Sterile (6,6-D2)-glucose stock (500 mg/mL)

Procedure:

1. Remove overfill (20 ml) of NaCl so that final volume is 250 mL. Use sterile needle and syringe.
2. Add 5.0 ml of sterile 2D-glucose stock. Mix.
3. Record lot number of NaCl

II. 20% dextrose infusion:

1. Add 4.0 mL of sterile 2D-glucose stock to 500 ml bottle of D20. Mix.
2. Record lot number of D20.

III. (6,6-2D)-glucose stock:

1. Record catalog and lot numbers of 2D-glucose
2. Weigh out 2D-glucose – 150 gm
3. Dissolve in sterile 0.9% NaCl (~200 ml); warm to 37° C if necessary.
4. Adjust final volume to 300 ml with 0.9% NaCl
5. Sterile filter (0.22 μm).
6. Aliquot into sterile tubes: 5 mL/tube.
7. Store aliquots at -5° to 5° C.
8. Test stock for pyrogenicity and sterility

Notes: All steps but for III.2. are performed in a certified Biosafety cabinet under sterile conditions.