A randomised, double-blind, placebo-controlled, multicentre, Phase 3 study evaluating efficacy and safety of lanifibranor followed by an active treatment extension in adult patients with non-cirrhotic non-alcoholic steatohepatitis (NASH) and fibrosis 2 (F2)/fibrosis 3 (F3) stage of liver fibrosis

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This study has been transitioned to CTIS with ID 2023-508248-23-00 check the CTIS register for the current data. Primary objectivesThis Phase 3 study is conducted to evaluate lanifibranor in adults with NASH and liver fibrosis and consists of 2…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON56041

Source
ToetsingOnline

Brief title
Nativ3

Condition

- Hepatic and hepatobiliary disorders

Synonym
Liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Inventiva S.A.
Source(s) of monetary or material Support: Inventiva S.A.

Intervention

Keyword: double-blind, lanifibranor, non-cirrhotic non-alcoholic steatohepatitis (NASH)

Outcome measures

Primary outcome

PRIMARY EFFICACY ENDPOINTS

The primary endpoint will be a binary composite endpoint derived from the Week 72 liver biopsy as compared to the Baseline biopsy among patients randomised in the main cohort, i.e. at least the first 882 randomised, histologically eligible patients* (Responder/Non-responder):

Resolution of NASH and improvement of fibrosis at Week 72, defined by NASH Clinical Research Network (NASH CRN) scores for ballooning of 0 and inflammation of 0 to 1, and fibrosis score >=1 stage decrease compared to Baseline as determined by a central biopsy reading process.

*Histologically eligible patients are defined as patients still meeting the histological eligibility criteria at the end of the DBPC period, based on the second reading of the Screening biopsy, i.e. according to the Steatosis-Activity-Fibrosis (SAF) score: Steatosis score >=1, Activity score: A3

or A4, Fibrosis score: F2 or F3.

Secondary outcome

SECONDARY EFFICACY ENDPOINTS

Key secondary efficacy endpoints

Two binary endpoints derived from the Week 72 liver biopsy for the following histological features of NASH, as determined by a central biopsy reading process:

• Resolution of NASH and no worsening of fibrosis at Week 72, defined by NASH CRN scores for ballooning of 0, inflammation of 0 to 1, and no increase in fibrosis score when compared to Baseline

• Improvement of fibrosis and no worsening of NASH at Week 72, defined by a decrease in NASH CRN fibrosis score >=1 stage from Baseline and no increase in scores for ballooning, inflammation, or steatosis

Other secondary endpoints

• Several binary endpoints for the following histological features of NASH:

o Improvement of NASH CRN fibrosis stage by at least 2 points and no worsening of NASH (no increase in scores for steatosis, ballooning, or lobular inflammation) at Week 72

o Resolution of fibrosis, defined as NASH CRN fibrosis stage 0, at Week 72

o Improvement of NAFLD activity score (NAS) by at least 2 points (at least a 1 point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis, at Week 72

o Improvement of each histological feature of NASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning) and no

worsening of fibrosis at Week 72

o Resolution of NASH and no worsening of steatosis and improvement of fibrosis at Week 72, defined by NASH Clinical Research Network (NASH CRN) scores for ballooning of 0 and inflammation of 0 to 1, no increase of steatosis and fibrosis score >=1 stage decrease compared to Baseline

o Resolution of NASH and no worsening of steatosis and no worsening of fibrosis at Week 72, defined by NASH CRN scores for ballooning of 0, inflammation of 0 to 1, and no increase in steatosis or fibrosis scores when compared to Baseline

o Improvement of NAFLD activity score (NAS) by at least 2 points (at least a 1 point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of steatosis and no worsening of fibrosis, at Week 72

o NASH resolution and improvement of fibrosis at Week 72 in the subgroup of diabetic patients.

• Change from Baseline in liver stiffness by elastography and in steatosis by controlled attenuation parameter (CAP) (only at sites with suitable equipment) (at all applicable visits during DBPC and ATE periods)

• Changes from Baseline in lipids (including but not limited to: total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides [TG], Apo A1, Apo B, total Apo C3, Apo C3 in HDL, Apo C3 in LDL, Apo C3 in very-low-density lipoprotein (VLDL), leptin) (at all applicable visits during DBPC and ATE periods)

• Change from Baseline on parameters of inflammation (hsCRP) (at all applicable visits during DBPC and ATE periods)

• Change from Baseline in liver tests (AST, ALT, GGT, ALP, direct and total

bilirubin) (at all applicable visits during DBPC and ATE periods)

• Health-related quality of life as assessed by the NASH validated Chronic Liver Disease Questionnaire (NASH-CLDQ), the Short Form 36 (SF-36) health survey questionnaire, and the Work Productivity and Activity Impairment Questionnaire (WPAI) (at all applicable visits during DBPC and ATE periods)

• Population PK modelling trough plasma levels of lanifibranor and its metabolites using a sparse sampling scheme (PK parameters include Cmax, Tmax, AUC, T1/2, CL/F, Vd/F, at all applicable visits during DBPC period)

Glycaemic parameters secondary endpoints

• Change from Baseline in glycaemic parameters (HbA1c, fasting plasma glucose (FPG), Fasting plasma insulin, Adiponectin, Fructosamine, Homeostatic Model Assessment for insulin resistance (HOMA IR)) (at all applicable visits during DBPC and ATE periods)

• In patients with an established type 2 diabetes mellitus (T2DM) diagnosis, at Baseline and at all applicable visits during the DBPC period:

o If Baseline glycated haemoglobin (HbA1c) >=6.5%:

* Binary endpoint where a responder is defined as HbA1c <6.5% at Week 12 and Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments between Week 12 and Week 24

* Change from Baseline in HbA1c and FPG

• In patients without an established T2DM diagnosis, at Baseline during the DBPC period:

o Time to new diagnosis of T2DM, as per the American Diabetes Association

criteria

o Occurrence of newly diagnosed T2DM

• In all patients, during the DBPC period:

o Time to introduction of new antidiabetic treatment (including insulin)

EXPLORATORY ENDPOINTS

• Change from Baseline in biomarkers related to NASH and fibrosis, including but not limited to: TIMP-1, hyaluronic acid, P3NP, ProC3, CK-18 M65, MMP2, MMP9 (at all applicable visits during DBPC and ATE periods).

• Change from Baseline in biomarker composite scores including but not limited to: FIB-4, ELF score (at all applicable visits during DBPC and ATE periods)

• During the DBPC period:

o Time to liver-related death

o Time to HCC

o Time to 4-point major adverse cardiovascular events (MACE)

• Time to first clinical outcome event during the DBPC period; defined as a composite endpoint of any of the following:

o Histological progression to cirrhosis (defined as histological confirmation of fibrosis score CRN F4)

o All-cause mortality

o Liver transplant

o Hepatic decompensation event(s) due to NASH cirrhosis including

* Ascites requiring treatment

* Hepatic encephalopathy/Altered mental status requiring therapy intervention

(new or dose change) or admission to the hospital

* Upper gastrointestinal bleeding due to portal hypertension, e.g. esophageal varices, gastric varices, portal hypertension gastropathy, GAVE (Gastric antral vascular ectasia)

o Model for End-Stage Liver Disease (MELD) score >=15 related to NASH cirrhosis

o Development of varices due to NASH cirrhosis requiring primary prophylaxis for bleeding

• In a subset of sites: for patients for whom LiverMultiScan® has been performed before screening and for less than 7 months before randomisation

o Change from pre-treatment in liver fat content (MRI-PDFF) at Week 72

o Binary endpoint where a responder is defined reaching a relative decrease in MRI-PDFF of >= 30% at Week 72

o Binary endpoint where a responder is defined as reaching an absolute decrease in MRI-PDFF of >= 5% at Week 72

o Binary endpoint where a responder is defined as reaching <= 5.0% MRI-PDFF at Week 72 (i.e., non-alcoholic fatty liver disease (NAFLD) resolution)

o Change from pre-treatment in corrected T1 relaxation (cT1) at Week 72

o Binary endpoint defined as reaching cT1 decrease > 80 ms at Week 72

o Binary endpoint defined as reaching cT1 <= 800 ms at Week 72

o Binary endpoint defined as reaching cT1 <= 875 ms at Week 72

SAFETY ENDPOINTS

• Adverse Events (AEs)

• Adverse Events of Special Interest (AESIs): hypoglycaemia, peripheral oedema,

heart failure, ovulation resumption, bone fractures, cholelithiasis, anaemia,

and aminotransferase elevation

• Serious adverse events including major adverse cardiovascular events (MACE;

cardiovascular death, non-fatal myocardial infarction, non-fatal stroke,

hospitalization for acute coronary syndrome)

• Physical examination

• Vitals signs

• Electrocardiogram (ECG)

• Safety laboratory evaluations

• In a subgroup of approximately 300 patients: 12-lead ECG at Screening, Week

4, and Week 12

• In a subgroup of approximately 300 patients: Bone densitometry by dual-energy

X-ray absorptiometry (DEXA) scan: at Baseline or Week 4, Week 72 and Week 120

when relevant

Study description

Background summary

As there are currently no active treatments available for NASH, the sponsor want to see how well Lanifibranor works as a treatment. The Lanifibranor binds to proteins which assists in the reduction of fat accumulation and liver inflammation in liver cells. This can lead to a stabilization of the scarring in your liver or even in a decrease. The latter will improve overall health of your liver and can induce beneficial metabolic changes. Doctors are not allowed to prescribe or use this medicinal product outside of research. To date more than 500 subjects have received lanifibranor in research studies.

Study objective

This study has been transitioned to CTIS with ID 2023-508248-23-00 check the CTIS register

for the current data.

Primary objectives
This Phase 3 study is conducted to evaluate lanifibranor in adults with NASH and liver fibrosis and consists of 2 sequential periods - an initial double-blind placebo-controlled period of minimum 72 weeks followed by a double-blind active treatment extension period of 48 weeks.
This study will include a main cohort of patients with Steatosis-Activity-Fibrosis (SAF) activity score of A3-A4 and liver fibrosis stage of F2-F3, and an exploratory cohort of patients who histologically screen failed from the main study, with SAF-A2 to A4 and liver fibrosis of any stage (F1 to F4).
The primary objectives of both periods in the main cohort are:
• Double-blind placebo-controlled (DBPC) period (Part A)
To assess the effect of lanifibranor compared to placebo on NASH resolution and improvement of fibrosis assessed by liver histology.
• Double-blind active treatment extension (ATE) period (Part B)
To assess the safety of lanifibranor beyond the DBPC period.

The secondary and exploratory objectives of both periods in the main cohort are:
Key secondary objectives of DBPC period
• To assess the effect of lanifibranor compared to placebo on NASH resolution and no worsening of fibrosis
• To assess the effect of lanifibranor compared to placebo on improvement of fibrosis with no worsening of NASH

Other secondary objectives of both periods
During the DBPC period, effect of the 2 doses of lanifibranor will be compared to placebo.
During the ATE period, effect of lanifibranor will be descriptively assessed between the 2 doses.
• To assess the effect of lanifibranor on other key histological features of NASH (only for DBPC period)
• To assess the effect of lanifibranor on NASH resolution and improvement of fibrosis in diabetic patients (only for DBPC period)
• To assess the effect of lanifibranor on liver tests
• To assess the effect of lanifibranor on glycaemic parameters
• To assess the effect of lanifibranor on lipid parameters
• To assess the effect of lanifibranor on markers of inflammation
• To assess the effect of lanifibranor on liver stiffness and steatosis assessed by elastography
• To assess the effect of lanifibranor on health-related quality of life
• To assess the safety of lanifibranor
• To assess population PK modelling through plasma levels of lanifibranor using sparse sampling scheme (only for DBPC period)

Exploratory objectives of both periods

• To assess the effect of lanifibranor on the risk of liver-related death (only for DBPC period)
• To assess the effect of lanifibranor on the risk of hepatocellular carcinoma (HCC) (only for DBPC period)
• To assess the effect of lanifibranor on major adverse cardiovascular events (MACE) (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalisation for acute coronary syndrome) (only for DBPC period)
• To assess the effect of lanifibranor on delaying NASH disease progression measured by a composite endpoint that includes progression to cirrhosis, liver-related clinical outcome events, or all-cause deaths (only for DBPC period).
• To assess the effect of lanifibranor on steatosis, inflammation and fibrosis assessed via LiverMultiScan®, in a subset of patients with available pre and post treatment measurements (only for DBPC period).
• To assess the effect of lanifibranor on non-invasive biomarkers related to NASH and fibrosis.

For the exploratory cohort, the primary objective is the safety evaluation of lanifibranor.
The secondary objectives of the main cohort apply for the exploratory cohort (except histological objectives) and are considered as exploratory objectives. Only the exploratory objective of the main cohort relative to biomarkers applies for the exploratory cohort.

Other specific objectives
In the exploratory cohort and in the subgroup of patients with histological fibrosis stage F4 on the screening biopsy, an interim analysis (IA) may be conducted. Details on this IA (contents and timing) will be provided in the Statistical Analysis Plan (SAP). The objective of this interim analysis will be to obtain exploratory data on safety and efficacy data of lanifibranor in this specific population that will provide valuable information for the design of a planned outcome study in patients with NASH and compensated cirrhosis.

Study design

This Phase 3, multinational, multicentre study consists of 2 sequential periods: an initial DBPC period of minimum 72 weeks (defined as Part A) followed by a double-blind active treatment extension period of 48 weeks (defined as Part B). The DBPC period will have an individual variable duration and will last until the last patient randomised in the main cohort completed Week 72 visit or until a maximum of 120 weeks, whichever happens first, to further collect placebo-controlled safety data in a DB manner.
After the completion of DBPC period, all patients will receive lanifibranor in a double-blind active treatment extension period of 48 weeks: all patients will be re-randomised at their end of DBPC period to keep blinding, patients on placebo will be allocated to one of the 2 lanifibranor-treatment arms and those already on lanifibranor will remain blinded and continue on their

treatment-arm. A same informed consent will be obtained for both DBPC and ATE periods of the study.
A total of approximately 1,000 patients will be randomised in the main cohort and approximately 200 patients* in the exploratory cohort, employing a 1:1:1 randomisation scheme (lanifibranor 800 mg/day or 1200 mg/day or matching placebo) in the DBPC period or employing a 1:1 randomisation scheme (lanifibranor 800 mg/day or 1200 mg/day) in the ATE period. Stratifying factors are T2DM status (absence, presence) and fibrosis stage (F2, F3) at baseline for the main cohort, and T2DM (absence, presence) and fibrosis stage (F1-F3, F4) at baseline for the exploratory cohort.
* Randomisation into the exploratory cohort will continue until enrolment in the main cohort is completed. Once a target of 200 patients is reached (including both F1-F3 and F4 fibrosis stages), or the sample size of the main cohort is achieved, only those currently in screening may be enrolled. The patients with fibrosis stage F4 are expected to provide informative data for a planned outcome study in patients with NASH and compensated cirrhosis.
In the exploratory cohort and in this specific subgroup of patients with fibrosis stage F4 on the screening biopsy, an interim analysis may be conducted and details (contents and timing) of this interim analysis will be provided in the SAP. A data integrity plan will be developed detailing how the blinding is maintained, how integrity of the trial will be protected and to ensure continued adherence to treatment and trial retention in the subgroup of patients with fibrosis stage F4.

Intervention

In Part A of the study there will be 3 groups of patients who will receive either lanifibranor (800 mg/day or 1200 mg/day) or matching placebo. You may receive a placebo which looks like lanifibranor but contains no medication, and therefore is not expected to have any effect, to allow the Sponsor to see if lanifibranor works as well as or better than placebo. In Part B, no patients will receive placebo and all patients will receive either lanifibranor 800 mg/day or 1200 mg/day.
The group you are in will be selected at random. This means that you will be assigned by chance (like flipping a coin) to receive placebo or one of the two different doses of the study medication. For Part A, you will have one chance out of three of receiving lanifibranor 800 mg or lanifibranor 1200 mg or placebo, referred to as *study medication* for the rest of this information sheet. For Part B, you will have one chance out of two of receiving lanifibranor 800 mg or lanifibranor 1200 mg. In this study, neither you nor your investigator will know what treatment you are receiving.

Study burden and risks

The medicinal product to be investigated may cause side effects.
We do not know all the possible side effects of the study medication. Like all

medicines, the study medication can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some people may experience severe side effects and may require treatment.
The following side effects have been experienced by other patients with NASH who have taken the study medication in a phase 2 study called NATIVE:
- Very frequent (more than 10%): diarrhoea, fatigue
- Frequent (between 1 and 10%): nausea, weight increased, oedema peripheral (bilateral ankles oedema), headache, abdominal pain, dizziness, anaemia, constipation and increase in your liver enzymes.

The medicinal product can also have side effects that we do not know about at the moment.

Other risks
As with taking any drug, there is a risk of allergic reaction. Symptoms of allergic reactions are:
• Rash
• Wheezing and difficulty with breathing
• Dizziness and fainting
• Swelling around the mouth, throat or eyes
• A fast pulse
• Sweating
An increase in liver tests has been noted in a few patients, in particular in patients with a tendency to suffer from autoimmune disease. Patients with a personal or close family history of autoimmune liver disease, or a personal history of autoimmune thyroid disease may be more at risk of experiencing these elevations in liver tests.

During Part A, you will attend a maximum of 10 on-site study visits (Screening visit / Week 0, 4, 12, 24, 36, 48, 72, 96 and 120) and 3 phone visits at Week 60, 84 and 108. During the Week 72 visit, a liver biopsy will be done. A final Follow-up visit will occur 4 weeks later (only if you do not continue in Part B) which will conclude your participation in Part A of the study.
During Part B of the study, you will come to the study site for a maximum of 5 visits after the last visit of Part A (4, 12, 24 and 48 weeks and Follow-up visit) and the study team will plan 1 phone visit at 36 weeks after the last visit of Part A.
Patients will be required to fast before each visit and will have between 25 and 40 mL of blood drawn per in-person visit.

Overall, the three PPAR isoforms play an important role in several components of NASH from hepatic triglyceride accumulation to fibrosis. Preliminary findings from a Phase 2b study with lanifibranor in patients with noncirrhotic NASH with fibrosis demonstrated substantial improvement across multiple clinically significant endpoints (histological endpoints, liver enzymes, lipids and glucose metabolism), making such drug potentially beneficial in the

treatment of NASH.

There will also be additional liver tests:
- For Part A at Week 8, 18, 30 and then at least every 6 weeks after Week 36 (i.e. W42, W54, W60, W66, W78, W84, W90, W102, W108, W114)
- For Part B at 8 weeks, 18 weeks, 30 weeks after the last visit of Part A and then at least every 6 weeks until the end of the study (i.e. 36 weeks, 42 weeks after last visit Part A)
These additional liver tests will involve the collection of blood samples at the hospital. or through an accessible laboratory nearby (with proper supervision of the investigator) arranged by the hospital.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

To be eligible to be screened for the study, potential patients must meet one of the following criteria (See Section 13.5):

1. Diagnosed with NASH on prior liver biopsy by local pathology reading excluding those read as F4 fibrosis (can have been any time in past for this qualification purpose)
2. Type 2 diabetes with high waist circumference or obesity, or hepatic steatosis on ultrasound
3. At least three of the following components of metabolic syndrome:
o High waist circumference or obesity, or hepatic steatosis on ultrasound
o Type 2 diabetes
o Low HDL cholesterol
o High triglyceride level
o Arterial hypertension

Inclusion criteria:
For randomisation of an eligible patient, all inclusion criteria must be answered *yes* at the time of Screening and re-confirmed at Baseline (i.e., before randomisation), except for laboratory tests for which Screening results are used for randomisation. If information is not able to be confirmed in the medical record, responses will be obtained in a patient interview:
1. Able to understand the nature of the study, willing and able to comply with the study procedures and restrictions, and able to provide signed, dated and written informed consent obtained before any study-related activities, sampling and analysis.
2. The patient will be willing to continue on the study in case of moving or relocation during the first 72 weeks of the study.
3. Male or female, aged >=18 years at the time of signing informed consent
4. If biopsy is performed before Screening, i.e. if a historical biopsy is available, a histological diagnosis of NASH with liver fibrosis must be made no more than >7 months before randomisation.
5. Main cohort: Upon central biopsy reading process: diagnosis of NASH according to the Steatosis-Activity-Fibrosis (SAF):
a) Steatosis score >=1
b) Activity score: A3 or A4
c) Fibrosis score: F2 or F3
This SAF-based diagnosis translates into the following CRN NAS-based diagnosis:
• CRN-Steatosis score >=1, CRN-Inflammation (CRN-I) score >=1 and CRN-Ballooning (CRN-B) score >=1
• NAS score >=5, or [NAS score >=4 with either CRN-I >=2 or CRN-B >=2]
• CRN-Fibrosis score: F2 or F3

Exploratory cohort: Patients who, upon central biopsy reading process, do not meet the eligibility criteria described above but fulfil the following criteria: diagnosis of NASH according to the Steatosis-Activity-Fibrosis (SAF):
a) Steatosis score >=1
b) Activity score >=2 with SAF-Inflammation score >=1 and SAF-Ballooning score >=1
c) Fibrosis score: any stage (F1 to F4)

6. MELD score <=12 (unless patient is on anticoagulants)

7. For patients receiving the concomitant medications listed below: no qualitative change in dose are allowed (changes having minimal clinical impact like temporary cessation/change between class of drugs are allowed), for the specified period prior to the qualifying liver biopsy and dose must remain stable from the time of the liver biopsy until the Baseline visit (Visit 0):
a) Antidiabetic treatment if glucagon-like peptide-1 receptor agonists (GLP1 receptor agonists including combinations) or sodium-glucose co transporter-2 inhibitors (SGLT2 inhibitors): for at least 3 months
b) Vitamin E (if at a dose >=400 IU/day): for at least 6 months
c) Statins: for at least 3 months
d) Anti-obesity treatments for at least 6 months
8. For patients receiving concomitant medications not covered by criterion #7 and that may impact safety or efficacy evaluation (antidiabetic treatments other than GLP1 (or combinations) receptor agonists and SGLT2 inhibitors, antihypertensives, antidepressants, cardiovascular, antihyperlipidemic) no qualitative change in dose are allowed for at least 3 months prior to the Baseline visit (Visit 0)
9. For overweight/obese patient, history of at least 1 unsuccessful attempt to reduce body weight by diet and/or exercise within the past 6 years
10. Weight stable for 6 months prior to Screening and between the qualifying liver biopsy and Baseline (no more than 5% change for both periods)
11. Criterion removed from Version 3.0 on
12. Patient agrees to follow recommendations with lifestyle modifications, which will be monitored throughout the whole study period.
13. Negative serum pregnancy test at study Screening for females of childbearing potential confirmed by central laboratory. Females of childbearing potential must practice a consistent and proper use of highly effective method of contraception throughout the study and for 1 month after treatment discontinuation. Highly effective contraceptive methods are defined as follows: combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that partner is the sole sexual partner of the female patient and that the vasectomised partner has received medical assessment of the surgical success), or sexual abstinence (intended as true abstinence when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception). Female patients who are only in same-sex relationships are not required to use contraception.

Exclusion criteria

For randomisation of an eligible patient, all the following exclusion criteria

must be answered *no* at Screening and re-confirmed at Baseline (i.e. before randomisation), except for laboratory tests for which Screening results are used for randomisation:
Liver-related:
1. Documented causes of chronic liver disease other than NASH including, but not restricted to:
a) Viral hepatitis documented with
i. Positive hepatitis B surface antigen (HBsAg)
ii. Positive hepatitis C virus ribonucleic acid (RNA) (tested for in case of known cured hepatitis C virus [HCV] infection or positive HCV serology at Screening). Patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years.
b) Drug-induced liver disease
c) Alcoholic liver disease: patients with a history of alcohol use who present an AST:ALT ratio of >=2 and gamma-glutamyltransferase (GGT) >2 × upper limit of normal (ULN) and macrocytosis with mean corpuscular volume (MCV) >95 fL without known aetiology of Vitamin B12 insufficiency
d) Autoimmune hepatitis (see Exclusion criteria 44 for more information)
e) Wilson*s disease
f) Haemochromatosis
g) Primary biliary cholangitis
h) Primary sclerosing cholangitis
i) Alpha-1-antitrypsin deficiency
j) Chronic portal vein thrombosis or splenic vein thrombosis
2. Histologically documented liver cirrhosis in the most recent historical biopsy (fibrosis stage F4) or suspicion at Screening of cirrhosis based on clinic biochemical and imaging criteria upon investigator*s assessment (see Section 9.1.1)
3. History or current diagnosis of hepatocellular carcinoma (HCC)
4. History of or planned liver transplant
5. Inability or unwillingness to undergo a liver biopsy at Screening (if a suitable historical biopsy is unavailable for central review) and at Week 72
6. Positive human immunodeficiency virus (HIV) serology
7. ALT or AST >5 × ULN
7.1. AST < 0.60 × ULN if the screening liver biopsy has to be performed in the scope of the study
7.2. Liver Stiffness Measurement (LSM) < 6 kPa by transient elastography (or equivalent) during screening if the screening liver biopsy has to be performed in the scope of the study.
8. Abnormal synthetic liver function of any of the following:
a) Albumin below the lower limit of the normal range
b) International normalised ratio (INR) >=1.3 (unless patient is on anticoagulants)
c) Total bilirubin level >=1.5 mg/dL (25.6 µmol/L). Patients with a history of Gilbert*s syndrome can be enrolled if the direct bilirubin is <=0.45 mg/dL (7.7 µmol/L)
9. Haemoglobin < 110 g/L (11g/dL) for females and <120 g/L (12g/dL) for males

10. Leucocytes count < LLN. A lower count is acceptable in patients with benign ethnic neutropenia, if considered to be clinical insignificant by the investigator.
11. Platelet count <140,000/µL
12. Alkaline phosphatase (ALP) >2 × ULN
13. Patient currently receiving any approved treatment for NASH
14. Current or recent history (<5 years) of significant alcohol consumption, which is typically defined as higher than 30 g pure alcohol per day for men and as higher than 20 g pure alcohol per day for women (please also refer to Section 13.1). No binge drinking during the last year. Consuming 75 g pure alcohol (male), or 60 g pure alcohol (female), or more in about 2 hours
15. Treatment with drugs that may cause non-alcoholic fatty liver disease (NAFLD) administered for at least 2 weeks within 12 months prior to qualifying liver biopsy (e.g. valproic acid, tamoxifen, methotrexate, amiodarone, oral corticosteroids >5 mg/day of prednisone equivalent, or oestrogens [at doses greater than those used for contraception or hormone replacement])
Glycaemia related:
16. HbA1c >9% at Screening
17. Diabetes mellitus other than type 2 (e.g. type 1, endocrinopathy, and genetic syndromes)
18. Current treatment with insulin
19. Treatment with PPAR-gamma agonists (e.g. thiazolidinediones [TZDs]) 12 months before randomisation, or any history of stopping TZD due to safety reason, e.g. weight gain or anaemia
Obesity related:
20. Bariatric surgery: restrictive procedures (e.g. lap banding, intragastric balloon, sleeve gastrectomy) are allowed, if performed >6 months prior to the qualifying liver biopsy; malabsorptive procedures (e.g. biliopancreatic diversion) and procedures combining both restrictive and malabsorptive methods (e.g. Roux-en-Y gastric bypass, duodenal switch surgery) are not allowed within 5 years of the qualifying liver biopsy. Liposuction and/or abdominoplasty are allowed if performed >6 months before qualifying liver biopsy. Planned bariatric surgery is not allowed.
21. New participation in an organised weight loss programme (e.g. Weight Watchers®, Jenny Craig®) within 6 months of the study, or planned participation through Week 72 or current treatment with orlistat.
Cardiovascular related:
22. History of heart failure with reduced left ventricular ejection fraction (LVEF) defined as any past measurement of LVEF <= 40%.
23. N-terminal-prohormone B-type natriuretic peptide (Nt-proBNP) >900 pg/mL.
24. Atrial fibrillation requiring anticoagulation
25-43. Refer to protocol for full list
Autoimmune related:
44.Any patient with a predisposition to autoimmune liver disease, incl:
a)Signs on liver biopsy suggestive of autoimmune liver disease
b)Family history of autoimmune liver disease in a first degree relative
c)Autoimmune thyroid disease

1.Diagnosis of autoimmune thyroid disease
2.Thyroid replacement hormone unless documented for reason of primary thyroid insufficiency
3.Positive autoimmune antibodies associated with abnormal thyroid function testing (TSH, T4 or free T3)
i.Anti-thyroid peroxidase antibody (TPO) or
ii.Anti-TSH receptor antibodies (TRAb)
d)History of or positive testing at screening for:
1.Anti-nuclear antibodies (ANA) at a dilution of 1:320 or greater
2.Anti-mitochondrial antibodies (AMA)
3.Anti-smooth muscle antibodies (ASMA) at a dilution of 1:320 or greater
4.Anti-liver kidney microsomal type 1 antibodies (LKM1)
5.Anti-liver cytosol type 1 antibody (LC1)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-12-2021
Enrollment:	25
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine

Brand name:	Lanifibranor
Generic name:	na

Ethics review

Approved WMO Date:	30-09-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	06-12-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-06-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-07-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-08-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-09-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2022
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-09-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-12-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-01-2024
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-02-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-04-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508248-23-00
EudraCT	EUCTR2020-004986-38-NL
ClinicalTrials.gov	NCT04849728
CCMO	NL78613.028.21