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

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1. Primary Objective The primary objective of this study is to assess the effect of lanifibranor alone compared toplacebo and the effect of lanifibranor in combination with empagliflozin compared to placeboon HbA1c after a 24-week treatment duration…

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

Summary

ID

NL-OMON53417

Source
ToetsingOnline

Brief title
LEGEND study

Condition

- Hepatic and hepatobiliary disorders
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Diabetes type 2, diabetes; Non-alcoholic Steatohepatitis, liver inflammation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Empagliflozin, Lanifibranor, Non-cirrhotic non-alcoholic steatohepatitis (NASH), Proof-of-concept

Outcome measures

Primary outcome

The primary efficacy endpoint of this study is the absolute change in HbA1c

from baseline

(Week 0) to Week 24.

Secondary outcome

The following secondary endpoints will be evaluated at Week 24:

* Change from baseline to Week 24 in liver tests (ALT, AST, GGT, ALP, total and

direct

bilirubin)

* Change from baseline to Week 24 in markers of glycemic control and insulin

resistance

(determination of hepatic insulin sensitivity, HOMA-IR, fasting insulin, FPG,

fructosamine, adiponectin)

* Binary endpoint defined as reaching HbA1c < 7.0% at Week 24, and no new

antidiabetic treatment or increase in dosages of antidiabetic treatments

* Binary endpoint defined as reaching HbA1c decrease >= 0.5% at Week 24, and no new antidiabetic treatment or increase in dosages of antidiabetic treatments

* Change from baseline to Week 24 in inflammatory markers (hsCRP, IL-6, IL-1β)

* Change from baseline to Week 24 in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, TG)

* Change from baseline to Week 24 in body weight

* Binary endpoint defined as reaching body weight increase >= 5% at Week 24

* Change from baseline to Week 24 in body composition as determined by MRI (including but not limited to: VAT, SAT, thigh SAT)

Study description

Background summary

NASH is a liver disease associated with inflammation and injury of the liver cells. NASH may lead to scarring of the liver and even causing so much damage to the liver that it does not work properly anymore. Once you have developed advances scarring of the liver, the serious complications may occur, including liver failure. NASH might also lead to liver cancer. At this time, there are no drugs approved for the treatment of NASH.
Diabetes is a disorder that disrupts the normal process of converting food to energy. Patient with diabetes have high blood sugar (glucose) levels. In diabetes, the major hormone that controls blood glucose (insulin) no longer functions optimally (*insulin resistance*). This insulin resistance causes not only diabetes but can also be associated with the development of NASH.
The sponsor is running a study to investigate drugs that may potentially help both NASH and diabetes. Lanifibranor is a new medication being investigated in clinical trials in patients with NASH. 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 improve your metabolism (process of producing energy and basic materials needed

for important life processes). Empagliflozin is a medicine approved for the treatment of diabetes in Europe under the trade name Jardiance®.

Study objective

1. Primary Objective
The primary objective of this study is to assess the effect of lanifibranor alone compared to
placebo and the effect of lanifibranor in combination with empagliflozin compared to placebo
on HbA1c after a 24-week treatment duration.
In line with ICH E9 (R1) addendum, five attributes (treatment, population, endpoint,
intercurrent events, and population-level summary) were specified to translate the primary
efficacy objective into treatment effects that are to be estimated (estimands).
The primary estimand is the comparison of lanifibranor alone and lanifibranor plus
empagliflozin versus placebo on the change in HbA1c from baseline to end of treatment
(Week 24), on the population initiating treatment with lanifibranor or lanifibranor plus
empagliflozin, and excluding potential rescue medication (under the hypothetical strategy
where patients would have continued their treatment during 24 weeks without rescue
medication).

2. Secondary Objectives
The secondary objectives of this study are to assess the effect of lanifibranor alone compared
to placebo and lanifibranor in combination with empagliflozin compared to placebo after a
24-week treatment duration on:
* Liver tests
* Markers of glycemic control and insulin resistance
* Inflammatory markers
* Lipid parameters
* Body weight and body composition
and to assess the safety and tolerability of lanifibranor alone and in combination with
empagliflozin during the 24-week treatment period and the 4-week follow-up period.

3. Exploratory Objectives
Exploratory objectives of this study are to assess the effect of lanifibranor alone compared to

placebo and lanifibranor in combination with empagliflozin compared to placebo after a
24-week treatment duration on:
* Hepatic fat content measured by a well-established (MRI-PDFF) technique known as IDEAL
* Steatosis, inflammation and fibrosis assessed via LiverMultiScan®
* Non-invasive biomarkers related to NASH and fibrosis (included but not limited to:
TIMP-1, hyaluronic acid, P3NP, CK18M30 and M65, proC3)
* Liver elasticity and tissue attenuation quantified by Velacur
TM
ultrasound system (only applies to sites where VelacurTM is available)
* LSM performed by elastography, CAP and FAST (Fibroscan-AST) score quantified by
FibroScan®
* The time from baseline to initiation of a rescue medication
* To perform popPK modelling of lanifibranor.

Study design

This proof-of-concept study will assess the safety and efficacy of the pan-PPAR agonist lanifibranor alone and in combination with the SGLT2 inhibitor empagliflozin in patients diagnosed with NASH and T2DM. The study is designed as a multinational, multicenter, three-arm, randomized, double-blind for lanifibranor and placebo, open-label for the combination lanifibranor plus empagliflozin, placebo-controlled, 24-week treatment study followed by a 4-week post-treatment follow-up visit. A total of 63 patients are planned to be randomized 1:1:1 to receive lanifibranor alone, or lanifibranor plus empagliflozin, or placebo. An interim analysis (IA) will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier, that will constitute the Interim Analysis Set (IAS). At this time, all protocol-defined analyses will be performed. A data integrity plan will be developed detailing, among the patients not belonging to the IAS, how the blinding is maintained, how integrity of the trial will be protected and to ensure continued adherence to treatment and trial retention.
The objective of this interim analysis will be:
• To obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints, helping supporting future decision making, both for the LEGEND study and in the overall lanifibranor clinical program
• To stop recruitment should clear trends in study findings be observed thereby minimizing patient exposure with additional patients
• To evaluate early signs on the impact on mechanistic endpoints, to determine whether to continue to perform more complex

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

Intervention

The study will have 3 groups of patients who will receive the following:
Double-blinded:
Group 1: Lanifibranor (800 mg/day, 1x daily 2 tablets)
Group 2: placebo (1x daily 2 tablets)
Open label:
Group 3: Lanifibranor (800 mg/day, 1x daily 2 tablets) plus Empagliflozin (10 mg/day, 1x daily 1 tablet)

Study burden and risks

Please see protocol section 2.3 Risk/Benefit assessment.
Please see section 6.0 in the Main ICF for possible side effects and complications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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

acceptable methods of contraception.

Exclusion criteria

Liver-related:
1. Documented causes of chronic liver disease other than NASH (see protocol for details, see exclusion criteria no 50 for autoimmune diseases)
a. Viral hepatitis, documented with
i. Positive hepatitis B surface antigen (HBsAg)
ii. Positive hepatitis C virus ribonucleic acid (RNA) (tested for in case of known cured hepatitis C virus [HCV] infection or positive HCV serology at Screening). Patients with a history of HCV infection can be included if HCV PCR is negative since more than 3 years.
b. Drug-induced liver disease
c. Autoimmune hepatitis
d. Wilson*s disease
e. Hemochromatosis
f. Primary biliary cholangitis
g. Primary sclerosing cholangitis
h. *1-antitrypsin deficiency
2. Histologically documented liver cirrhosis (fibrosis stage F4), based on a historical biopsy (within 12 months prior to Screening); or diagnosis of cirrhosis at Screening based on clinic biochemical and imaging criteria (FibroScan® value confirmed >= 14 kPa and FIB-4 > 3.25 provided to the site by the central lab)
3. History or current diagnosis of hepatocellular carcinoma (HCC)
4. History of or planned liver transplant
5. Documented history of human immunodeficiency virus (HIV) infection
6. ALT or AST > 5 × upper limit of normal (ULN) at Screening
7. Abnormal liver function as defined by central laboratory evaluation of any of the following:
a. Albumin < lower limit of normal range (LLN)
b. International normalized ratio (INR) >= 1.3 (unless patient is on anticoagulants)
c. Total bilirubin level >= 1.5 mg/dL (25.7 µmol/L) (Patients with a documented history of Gilbert*s syndrome can be enrolled if direct bilirubin is <= 0.45 mg/dL (7.7µmol/L))
8. Hemoglobin < 110 g/L (11 g/dL) for females and < 120 g/L (12 g/dL) for males
9. White blood cell count (WBC) < LLN. A lower count is acceptable in patients with benign ethnic neutropenia, if considered to be clinical insignificant by the investigator.
10. Platelet count < 140,000/µL
11. Alkaline phosphatase (ALP) > 2 × ULN
12. Patient currently receiving any approved treatment for NASH or obesity
13. Current or recent history (< 5 years) of significant alcohol consumption,

which is typically defined as higher than 30 g pure alcohol per day for men and as higher than 20 g pure alcohol per day for women (please also refer to Section 13.1). No binge drinking during the last year. Consuming 75 g pure alcohol (male), or 60 g pure alcohol (female), or more in about 2 hours
14. Administration of drugs known to produce hepatic steatosis in the 6 months prior to Screening (such as high-dose estrogens, methotrexate, tetracycline, or amiodarone) (see also Section 13.2)

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

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

Cardiovascular related:
24. History of (within 3 months prior to Screening) or current unstable cardiac dysrhythmias
25. NT-proBNP > 900 pg/mL
26. Unstable heart failure including:
a. New, or worsening symptoms of coronary heart disease within the past 3 months prior to Screening
b. Acute coronary syndrome within the past 6 months prior to Screening
c. Acute myocardial infarction in the past 3 months prior to Screening
d. Heart failure of New York Heart Association class (III-IV) or worsening congestive heart failure, or coronary artery intervention, within the past 6 months prior to Screening
27. Any other clinically significant cardiovascular event requiring

hospitalization within 6 months before Screening
28. Uncontrolled hypertension at Screening (systolic blood pressure [SBP] > 160 mmHg and/or diastolic blood pressure [DBP] > 100 mmHg (under conditions described in Section 8.2.3.)
29. Stroke or transient ischemic attack within 6 months prior to Screening

General safety:
30. Significant systemic or major illnesses other than liver disease, (including but not limited to those listed above) and pulmonary disease, organ transplantation, serious psychiatric disease, that, in the opinion of the Investigator, would preclude treatment with lanifibranor and/or empagliflozin and/or adequate follow-up
31. Any condition which, in the Investigator*s opinion, might jeopardize a patient*s safety or compliance with the protocol, or warrants exclusion from the study
32. Cancer: Presence or history of malignancy within 5 years prior to Screening and/or active neoplasm at Screening. History of cancer is allowed only following 5 years of documented remission with the exception of resolved superficial nonmelanoma skin cancer
33. History of bladder disease and/or persistent hematuria within 6 months prior to Screening (transient hematuria which has been documented to have resolved within one week is acceptable), or current hematuria unless due to a urinary tract infection
34. Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value < 60 mL/min as determined by Modification of Diet in Renal Disease [MDRD]
35. Total creatine kinase > 1.5 x ULN
36. History of pancreatitis, or confirmed pancreatic lipase > 1.3 x ULN, or > 2.0 x ULN upon repeated test within 3 weeks if on a DPP-IVi
37. Concomitant treatment with PPAR-* agonists (fibrates); if treatment with PPAR-* agonist is discontinued before the Baseline visit, it should be anticipated that triglycerides remain < 500 mg/dL during the study
38. Patients on Vitamin E at doses >= 400 IU/day; doses of >= 400 IU/day are allowed when no qualitative change in dose for 6 months prior to Screening
39. SARS CoV 2 infections requiring hospitalization in the last 3 months or current SARS CoV 2 infection confirmed by a validated test. (A SARS CoV 2 test is not required for all patients at Screening visit but will be performed according to local standard practice). In case of previous asymptomatic or mild SAR CoV 2 infection, the investigator should verify that abnormal lab tests due to COVID 19 are back to pre COVID 19 status before patient randomization.
40. Major surgery scheduled during the study
41. Known or suspected hypersensitivity to any of the ingredients of the investigational medicinal products (IMPs)
42. Rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
43. Previous exposure to lanifibranor or empagliflozin
44. Osteopenia, or any other documented bone disease. Patient without documented osteopenia treated with vitamin D and/or calcium-based supplements

for preventive reasons can be included.
45. Claustrophobia to a degree that prevents tolerance of MRI scanning procedure. Sedation is permitted at discretion of the Investigator.
46. Metallic implant of any sort that prevents MRI examination including, but not limited to: aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, tattoo, body piercing that cannot be removed, cochlear implant; or any other contraindication to MRI examination
47. Present pregnancy/lactation or inability to adhere to adequate contraception in women of childbearing potential
48. Treatment with strong inducers or inhibitors of CYP2C8. When administered chronically, they should be replaced 3 months before Screening visit. If not administered chronically, they should be stopped at least 7 days before treatment initiation (See Section 6.7 and Section 13.2). Prior administration of other drugs (i.e. weight loss treatments, chronically administered medications) as specified in Section 13.2.
49. Participation in any clinical trial of an approved or non approved investigational medicinal product/device within 3 months from Screening or five half-lives of the investigational drug from Screening, whichever is longer. Participation in non-interventional trials will be allowed with Sponsor approval.

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

Study design

Design

Study phase:	2
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):	24-01-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Jardiance
Generic name:	Empagliflozin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Lanifibranor

Ethics review

Approved WMO Date:	15-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2022

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2021-005057-87-NL
ClinicalTrials.gov	NCT05232071
CCMO	NL81473.018.22