A 12-week randomized, patient and investigator blinded, placebo-controlled, parallel group study to investigate the efficacy of LIK066 in obese patients with non-alcoholic steatohepatitis (NASH)

Published: 16-10-2017
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Primary objective:- To determine the effect of LIK066 on Liver Function test after 12 weeks of treatmentSecondary objectives: - To determine the effect of LIK066 on intrahepatic lipid after 12 weeks of treatment- To determine the effect of LIK066 on...

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

Summary

ID

NL-OMON44568

Source
ToetsingOnline

Brief title
Efficacy of LIK066 for the treatment of non-alcoholic steatohepatitis

Condition

- Hepatic and hepatobiliary disorders

Synonym
NASH, non-alcoholic steatohepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis AG

Intervention

Keyword: LIK066, non-alcoholic steatohepatitis (NASH), SGLT1 inhibitor, SGLT2 inhibitor

Outcome measures

Primary outcome

Change in circulating alanine aminotransferase (ALT) levels

Secondary outcome

- Percent (%) Liver fat as measured by Magnetic Resonance Imaging (MRI-PDFF)

- Percent change in total body weight

- Enhanced liver fibrosis panel (ELF: PIIINP, TIMP-1, and Hyaluronic acid)

- Adverse events, safety laboratory tests including basic chemistry profile and

liver biochemical tests

- Cmax, Tmax, AUClast

- Circulating aspartate aminotrasferase (AST) levels

Study description

Background summary

Obesity has become a major global health problem that contributes causally to and exacerbates many serious co-morbidities The presence of obesity and insulin resistance, often with clinical features of the metabolic syndrome, leads to a high-risk profile for the development of non-alcoholic fatty liver disease (NAFLD). NAFLD encompasses a broad spectrum of disease severity, ranging from isolated steatosis to its more
severe form with variable degrees of hepatocyte inflammation, necrosis and liver fibrosis, known as nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and end stage liver disease.

LIK066 is a potent inhibitor of the sodium glucose co-transporters 1 and 2 (SGLTs) that decreases absorption of glucose in the gut and reabsorption in the kidney, and is investigated for the treatment of obesity and type 2 diabetes mellitus.

The purpose of this study is to assess the effects of LIK066 on liver function tests (LFT) and a variety of metabolic and inflammation biomarkers in patients with NASH after 12 weeks of treatment. Data from this study will be used to support further development of LIK066 in the treatment of patients with NASH.

Study objective

Primary objective:
- To determine the effect of LIK066 on Liver Function test after 12 weeks of treatment

Secondary objectives:
- To determine the effect of LIK066 on intrahepatic lipid after 12 weeks of treatment
- To determine the effect of LIK066 on total body weight after 12 weeks of treatment
- To determine the effect of LIK066 on non-invasive markers of liver fibrosis after 12 weeks of treatment
- To determine the safety and tolerability of LIK066
- To evaluate the pharmacokinetics (PK) of LIK066 in NASH patients
- To determine the effect of LIK066 on circulating aspartate aminotransferase (AST) after 12 weeks of treatment

Exploratory objectives:
- To explore the effects of LIK066 on insulin sensitivity and glycemic control
- To explore the effects of LIK066 on markers of inflammation
- To explore the effects of LIK066 on changes in lipid metabolites
- To explore the effects of LIK066 on liver fibrosis biomarkers
- To explore the effects of LIK066 on pharmacogenetics in NASH patients (optional)
- To explore the effects of LIK066 on other relevant biomarkers
- To explore the effects of LIK066 on body fat compartments
- To determine the effect of LIK066 on fasting lipid profile
- To explore the effect of LIK066 on liver inflammation and/or fibrosis

Study design

This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study in patients with NASH. The study will consist of a screening period up to 28 days, baseline period up to 14 days, treatment period of 12 weeks followed up by a study completion

evaluation approximately 28 days after the final drug administration.

Intervention

Study treatments are defined as:
- 50 mg LIK066 tablets
- 10 mg LIK066 tablet
- Matching placebo tablets
Initially, patients will be randomly assigned to one of the following two treatments in a ratio of 2:1:
A: LIK066 150 mg
B: Matching placebo

Additional treatment arms (30 mg) may be introduced based on interim analysis results or at the sponsor*s request, after 33 patients have been enrolled into the initial 150 mg and matching placebo arms. If one additional dosing arm is included, patients will be assigned to one of the following three treatments (C, D or E) in a ratio of 2:4:1 using a new randomization schedule.
C: LIK066 150 mg
D: LIK066 30 mg
E: Matching placebo

Study burden and risks

Burden:
- time investment
- once daily intake of 3 oral LIK066 tablets or placebo during 12 weeks
- measurements including blood sampling and MRI
- compliance with strict lifestyle restrictions
- glucose measurements with a glucometer at home (possibly more than usual, both before and after start of LIK066 if needed)

Potential risks:
- potential side effects of LIK066
- potential complaints caused by being fasted (especially in patients with type 2 diabetes mellitus), blood sample collection and MRI

Potential benefits:
- contributing in understanding (the treatment) of NASH
- possible positive effect on liver function (yet unknown)
- decrease in body weight

Contacts

Public
Novartis

Lichtstrasse 35
Basel CH-4056
CH
Scientific
Novartis

Lichtstrasse 35
Basel CH-4056
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Presence of NASH as demonstrated by one of the following:
either
Histologic confirmed NASH based on liver biopsy obtained 2 years or less before randomization with a fibrosis level of F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases AND ALT * 50 IU/L (males) or * 35 IU/L (females) at screening;Or
Phenotypic diagnosis of NASH based on presence of all three of the following at screening:
- ALT * 50 IU/L (males) or * 35 IU/L (females) AND
- BMI * 27 kg/m2 (in patients with a self-identified race other than Asian) or *23 kg/m2 (in patients with a self-identified Asian race) AND
- Diagnosis of Type 2 diabetes mellitus by HbA1C: * 6.5% and * 10%

Exclusion criteria

- Use of GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide; SGLT-2 inhibitors such as canagliflozin, empagliflozin or dapagliflozin; Thiazolidinediones (TZDs) such as pioglitazone; FXR agonists such as obeticholic acid (OCA) and any pharmacologically active weight-loss medications such as lorcaserin prior to 6 weeks of screening visit and up to end of study visit
- eGFR * 45ml/min/1.73m2 based on MDRD equation
- Patients on treatment with the following medicines unless they are on a constant dose for *3 months before randomization: anti-diabetic medications, insulin (if *25% change in dose), beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 400 IU/day; doses > 800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control
- Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average)
- Presence of cirrhosis on liver biopsy or clinical diagnosis of cirrhosis
- Type I diabetes and uncontrolled diabetes defined as HbAlc > 10 % within 60 days prior to enrollment
- Patients with contraindications to MRI imaging
- For those patients that have had a previous liver biopsy:
Significant weight loss (>15%) or change in clinical status (in the opinion of the investigator) since the diagnostic liver biopsy to screening
- History or presence of other concomitant liver diseases
- Clinical evidence of hepatic decompensation or severe liver impairment
- History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline
- History of inflammatory bowel disease
- History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
- History of ketoacidosis, lactic acidosis, or hyperosmolar coma OR if occurring between Screening Visit and Randomization Visit.
- History of lower limb amputation (including toe amputation) OR if occurring between Screening Visit and Randomization Visit.

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:	Recruitment stopped
Start date (anticipated):	19-12-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LIK066
Generic name:	not applicable

Ethics review

Approved WMO Date:	16-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-01-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-10-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-002046-71-NL
ClinicalTrials.gov	NCT03205150
CCMO	NL63244.056.17