A randomized, double-blind, placebo controlled, 2- part, adaptive design, multicenter 12-week study to assess safety, tolerability and efficacy of LJN452 in patients with non-alcoholic steatohepatitis (NASH)

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To assess the safety and tolerability profile of LJN452 and to determine the early hepatic response to different doses of LJN452 in patients with phenotypic non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further...

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

Summary

ID

NL-OMON46032

Source
ToetsingOnline

Brief title
CLJN452A2202

Condition

- Hepatic and hepatobiliary disorders

Synonym
Extra amount of fat in liver cells that is not caused by alcohol use

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor / verrichter van het onderzoek).

Intervention

Keyword: efficacy, non-alcoholic steatohepatitis, safety

Outcome measures

Primary outcome

The primary objective of the study is to determine safety and tolerability of different doses of LJN452 by monitoring adverse events up to the end of the study. Moreover, the study will determine the dose-response relationship of LJN452 on markers of hepatic inflammation in NASH by changes in ALT and AST from baseline to Week 12. The study will also determine the dose-response relationship of LJN452 on liver fat content by changes in quantitative MRI determined fat.

Secondary outcome

- To determine the effect of different doses of LJN452 on anthropometric assessments (weight, BMI, waist-to-hip (WTH) ratio) after 12 weeks of treatment
- To determine the dose-response relationship of LJN452 on FGF19 over time, a marker of FXR target engagement in the gut, and C4, a marker of hepatic target engagement
- To determine the dose-response relationship of LJN452 on markers of liver fibrosis commonly available such as Fibroscan® (in a subset of patients), enhanced liver fibrosis panel (ELF), and fibrosis biomarker test (originally

known as Fibrotest®/ FibroSure®)

- To determine the dose-response relationship of LJN452 on GGT, a marker of cholestasis

- To determine the effect of LJN452 on fasting lipid profile To determine the pharmacokinetics (PK) of LJN452

- To determine the effect of LJN452 compared to placebo with respect to occurrence of potential itch based on a visual analog scale (VAS) rating scale

- To determine effects of LJN452 on primary endpoints in the subset of patients who have historical biopsy data, both overall and by subsets defined by fibrosis score and/or NAS score as feasible (based on the extent of available data)

Study description

Background summary

The purpose of the study is to learn whether it is safe to treat patients who have NASH with the study drug LJN452. The study will also learn about the effects of different doses of LJN452 on markers of liver swelling in patients with NASH.

The second purpose is the examination of biomarkers to help answer scientific questions related to LJN452 effect on cells or organs in the body, as well as impact on the disease. These samples will also be used to try to understand the disease better

In addition, these samples help to understand how the body absorbs, distributes, breaks down and gets rid of LJN452. This is commonly referred to as pharmacokinetics.

Study objective

To assess the safety and tolerability profile of LJN452 and to determine the

early hepatic response to different doses of LJN452 in patients with phenotypic non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further development of LJN452 in the treatment of patients with NASH

Study design

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose finding, 2-part, adaptive, 12-week study to assess the safety, tolerability and efficacy of four doses of LJN452 as compared to placebo in patients with non-alcoholic steatohepatitis (NASH).

Intervention

LJN452 10 *g, 30 *g, 60 *g, 90 *g or matching placebo treatment

Study burden and risks

Following the baseline visit, the patiënt will return to the study center at regular intervals to have their condition monitored and to receive new bottles with study medication. If participating in Part A of the study, the patient will return 1, 2, 4, 6, 8, and 12 weeks after starting study medication. If the patient will participate in Part B of the study, the patient will return 2, 4, 6, 8, and 12 weeks after starting study medication.

Assessments during study visit:
- Blood pressure, pulse
- Weight, waist and hip measurements
- Physical exam:
- ECG
- Questionnaires
- Blood samples
- Urine tests
- Pharmacokinetic blood samples:
- Fibroscan®:
- MRI
- Exploratory biomarker (genetic test)

Contacts

Public
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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Written informed consent must be obtained before any assessment is performed
- Male and female patients 18 years or older (at the time of the screening visit)
- Presence of NASH as demonstrated by ONE of the following:
o Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3 (i.e. fibrosis in the absence of established cirrhosis), no diagnosis of alternative chronic liver diseases AND
o ALT * 43 IU/L (males) or * 28 IU/L (females)
OR
o Phenotypic diagnosis of NASH based on presence of ALL THREE of the following:
- ALT * 60 IU/L (males) or * 40 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 having either:
* HbA1C * 6.5% or
* Drug therapy for Type 2 diabetes mellitus
- Liver fat * 10% at screening as determined by the central MRI laboratory
- Patients must weigh at least 40 kg (88 lb) and no more than 150 kg (330 lb) to participate in the study

Exclusion criteria

- Previous exposure to obeticholic acid (OCA)
- Patients taking medications prohibited by the protocol
- Pregnant or nursing (lactating) women
- 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) and/or a score on the AUDIT questionnaire *8
- Uncontrolled diabetes defined as HbA1c * 9.5% within 60 days prior to enrollment
- Presence of cirrhosis on liver biopsy or clinical diagnosis
- Clinical evidence of hepatic decompensation or severe liver impairment
- Previous diagnosis of other forms of chronic liver disease
- Patients with contraindications to MRI imaging

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):	02-05-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LJN452

Generic name:	LJN452

Ethics review

Approved WMO Date:	23-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2017
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-005215-33-NL
ClinicalTrials.gov	NCT02855164
CCMO	NL57299.078.16