Double-blind, randomised, placebo-controlled, phase IIb trial on the efficacy and safety of norursodeoxycholic acid tablets in patients with non-alcoholic steatohepatitis (NASH)

Published: 16-10-2019
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Primary objective:* To evaluate the efficacy of norursodeoxycholic acid (norUDCA) 1500 mg vs. norUDCA 1000 mg vs. placebo for the treatment of NASHSecondary objectiveTo study safety and tolerability (adverse events [AEs], laboratory parameters) of...

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

Summary

ID

NL-OMON55446

Source
ToetsingOnline

Brief title
Norursodeoxycholic acid vs. placebo in NASH

Condition

- Hepatic and hepatobiliary disorders

Synonym
liver damage - non-alcocholic steatohepatitis (NASH)

Research involving
Human

Sponsors and support

Primary sponsor: Dr. Falk Pharma GmbH
Source(s) of monetary or material Support: Dr. Falk Pharma GmbH

Intervention

Keyword: Non-alcoholic steatohepatitis (NASH), Norursodeoxycholic acid

Outcome measures

Primary outcome

Primary efficacy variable:

Resolution of NASH, assessed by centrally scored liver histology and no

worsening of fibrosis from baseline to EOT/withdrawal visit

AND/OR

Improvement of fibrosis and no worsening of NASH.

Secondary outcome

Secondary efficacy variables:

• Improvement of NASH and no worsening of fibrosis from baseline to

EOT/withdrawal

• Change in NAS from baseline to EOT/withdrawal visit

• ALT <= 0.8 ULN at EOT/withdrawal visit

Study description

Background summary

Up until now, the treatment of patients with non-alcoholic steatohepatitis (NASH) remains a challenge. NASH is a type of non-alcoholic fatty liver disease. It is often called a *silent* disease because most patients do not know they have it. NASH includes both a fatty liver and liver inflammation. Although the disease remains without symptoms most of the time, it can slowly

progress to end stage liver disease such as liver cancer and liver failure. It will probably be the most common indication of liver transplantation in the future.
There is not yet any accepted standard treatment that is able to stop or reverse the progression of NASH. Current treatment options include life-style modifications such as physical exercise, diet change, blood fat control and optimal diabetes mellitus control.
For medical treatment, only a few clinical investigations have been carried out to date. Long-term data on safety and efficacy on drugs tested are still missing.
By carrying out this clinical trial, the efficacy, safety and tolerability of two different dosages of norursodeoxycholic acid (norUDCA) tablets will be investigated.

Study objective

Primary objective:*
To evaluate the efficacy of norursodeoxycholic acid (norUDCA) 1500 mg vs. norUDCA 1000 mg vs. placebo for the treatment of NASH
Secondary objective
To study safety and tolerability (adverse events [AEs], laboratory parameters) of norUDCA

Study design

This is a double-blind, randomised, multi-centre, placebo-controlled, comparative, phase IIb trial. The trial will be conducted with three treatment groups in the form of a parallel group comparison and will serve to compare oral treatment with either 1500 mg/d or 1000 mg/d norUDCA tablets vs. placebo tablets for the treatment of NASH (in patients with and without diabetes mellitus type 2 [T2DM]).

Double-blind, randomised (1:1:1) treatment phase:

Patients with NASH (with and without T2DM) will be randomised to receive a 72-week, double-blind treatment with:
- Group A: Norursodeoxycholic acid 1500 mg once daily (OD)
3 norUDCA tablets à 500 mg
- Group B: Norursodeoxycholic acid 1000 mg OD
2 norUDCA tablets à 500 mg AND 1 placebo tablet
- Group C: 3 placebo tablets OD

Blinding is achieved by the application of the same number of tablets (verum and/or placebo) to each patient, i.e. each patient will receive a total of 3 tablets.

Intervention

The trial medication are tablets for oral use. 3 tablets should be taken every day in the morning during the treatment phase of 72 weeks (about 18 months).
Laboratory evaluations will be performed.
Liver biopsy assessment will be performed at the start of the study and at the end of the study.
Additionally, following optional assessments can be performed at indicated visits: Fibroscan, ARFI, MRI/MRS, vascular ultrasound, gut microbiota analysis of stool sample.

Study burden and risks

The time and events schedule summarizes the frequency and timing of the various measurments and can be found in the protocol V4.0
(pages 13 and 14).

The procedures performed as part of this clinical trial may be associated with risks or lead to discomforts: blood sampling, ECG, liver biopsy and ultrasound.

Medication should be taken during the treatment phase of 72 weeks (about 18 months). The medication concerns 3 tablets which should be taken each day in the morning.
Questionnaires should be completed at visits indicated in the time and events schedule in the protocol V4.0 on page 13 and 14.
No patient diary will need to be completed.

Diagnostic procedures and examinations exercised in this clinical trial are mostly routine or non-invasive procedures. Only at screening and end of treatment visits, liver biopsies will be taken for histological assessment. According to the current European Association of the Liver (EASL) guideline for the management of NAFLD, liver biopsy is essential for the diagnosis of NASH and is the only procedure that reliably differentiates fatty liver from NASH. The histological assessments will enhance the evidence of the trial and support the prognostic validity of other efficacy endpoints which are based on non-invasive techniques like serum-based inflammation and fibrosis markers or liver stiffness measured by elastography. Accordingly, a potential risk associated with liver biopsy sampling seems to be justified with regard to the patient population studied.
Due to the lack of an available standard therapy, it seems justified to introduce a placebo-arm in this clinical trial.

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

- Must be willing to participate in the study and provide written informed consent
- Male or female patients >= 18 and < 75 years
- Centrally assessed histological evidence of NASH and liver fibrosis
- Women of childbearing potential agree to use a highly effective method of birth control during the entire duration of the trial and for 4 weeks following the last dose of trial treatment

Exclusion criteria

• Patients taking prohibited medications

• Presence of liver cirrhosis
• Type 1 diabetes or uncontrolled Type 2 diabetes
• History or presence of any other significant concomitant liver diseases
• History of liver transplantation
• BMI > 45 kg/m^2
• Any known relevant infectious disease (e.g., active tuberculosis, acquired immunodeficiency syndrome [AIDS]-defining diseases)
• Abnormal renal function (glomerular filtration rate estimated from cystatin C < 30 ml/min) at screening visit
• Any active malignant disease (except for basal cell carcinoma)
• Existing or intended pregnancy or breast-feeding

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):	15-09-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	/
Generic name:	24-norursodeoxycholic acid or Norucholic acid

Ethics review

Approved WMO Date:	16-10-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-04-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-03-2023
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-003443-31-NL
CCMO	NL68510.041.19