Double-blind, randomised, placebo-controlled, phase II dose-finding study comparing different doses of norucholic acid tablets with placebo in the treatment of primary biliary cholangitis in patients with an inadequate response to ursodeoxycholic acid

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To evaluate the efficacy of two doses of norucholic acid vs. placebo for the treatment of primary biliary cholangitis (PBC) in patients with an inadequate response to ursodeoxycholic acid (UDCA).

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bile duct disorders
Study type	Interventional

Summary

ID

NL-OMON53827

Source
ToetsingOnline

Brief title
NCA vs. placebo in PBC

Condition

- Bile duct disorders

Synonym
chronic inflammation of the small bile ducts in the liver, PBC

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: norucholic acid, PBC, ursodeoxycholic acid

Outcome measures

Primary outcome

Mean relative change (%) in ALP between the baseline visit and the EOT visit

(Last Observation Carried Forward, LOCF).

Secondary outcome

• Proportions of patients with at least 10%, at least 20%, and at least 40%

reduction in ALP between baseline and EOT (LOCF),

• Proportion of patients with normalisation of ALP (< ULN) at any visit during

the treatment phase,

• Proportion of patients with bilirubin levels <0.6x ULN at any visit during

the treatment phase,

• Proportion of patients with partial normalisation of ALP (< 1.5x ULN) at any

visit during the treatment phase,

• ALP at each trial visit (screening to follow-up),

• Absolute and relative changes (%) of ALP from baseline to each visit up to

EOT (LOCF), and from EOT to the follow-up visit,

• Gamma-glutamyltransferase (γ-GT), AST, ALT, albumin, platelet count and total

and conjugated bilirubin levels at each trial visit (screening to follow-up),

• Absolute and relative changes (%) of γ-GT, AST, ALT, albumin, platelet count

and total and conjugated bilirubin levels from baseline to each visit up to EOT

(LOCF), and from EOT to the follow-up visit.

Study description

Background summary

The planned trial is expected to provide efficacy and safety data for NCA tablets in patients with PBC. The trial should provide additional information on a safe and effective dose from 1000 mg and 1500 mg tablets OD administered to humans. A treatment duration of 12 weeks is considered sufficient to detect changes in surrogate markers of the disease. All efficacious PBC treatments have shown an effect on ALP within 8 weeks, e.g. UDCA, OCA, and bezafibrate. Therefore, a potential treatment effect by NCA is expected to be also seen within 12 weeks.

Study objective

To evaluate the efficacy of two doses of norucholic acid vs. placebo for the treatment of primary biliary cholangitis (PBC) in patients with an inadequate response to ursodeoxycholic acid (UDCA).

Study design

Double-blind, randomized, placebo-controlled, phase II dosing study comparing different doses of norucholic acid tablets with placebo.

The screening period for the study lasts a maximum of 6 weeks. 90 eligible PBC patients will be randomized to norucholic acid or placebo. The duration of treatment is 12 weeks followed by a 4-week follow-up period.

The 3 treatment groups are:
• Group A. The people in this group are given 1500 mg of norUDCA once a day: 3 norUDCA tablets of 500 mg each.
• Group B. The people in this group are given 1000 mg of norUDCA once a day: 2 norUDCA tablets of 500 mg each and 1 placebo tablet.
• Group C. The people in this group are given 3 placebo tablets once a day.

Intervention

• Group A. The people in this group are given 1500 mg of norUDCA once a day: 3

norUDCA tablets of 500 mg each.
• Group B. The people in this group are given 1000 mg of norUDCA once a day: 2 norUDCA tablets of 500 mg each and 1 placebo tablet.
• Group C. The people in this group are given 3 placebo tablets once a day.

Study burden and risks

physical examination 7x
weight, length 7x
ultrasound upper abdomen 2x
ecg 3x
blood and urine tests 7x
pruritus and fatigue VAS 5x
PBC-40 questionnaire 2x

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

• Signed informed consent, • Male or female patients >= 18 and <= 74 years at screening, • PBC verified by at least 2 out of the following 3 criteria at screening: - Chronic cholestatic disease of at least 12 months duration, - Positive anti-mitochondrial antibody (AMA) titer or, if AMA negative or in low titer (< 1:80), presence of PBC-specific antibodies (anti-GP210 and/or anti-SP100 and/or antibodies against the major M2 components [PDC-E2, 2-oxo-glutaric acid dehydrogenase complex]), - Liver biopsy available for review and compatible with the diagnosis of non-cirrhotic PBC, • Ursodeoxycholic acid (UDCA) treatment for at least 12 months (with a stable dose for >= 3 months) prior to screening, • Women of childbearing potential agreeing 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, defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptive methods, some intrauterine devices (IUD), sexual abstinence, or vasectomized partner. Women of non-childbearing potential (surgically sterile [e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or postmenopausal with at least two years without spontaneous menses) may be included. The investigator is responsible for determining whether the patient has adequate birth control for trial participation.

Exclusion criteria

1. History or presence of other relevant concomitant liver diseases, including (list not exhaustive):
• Positive hepatitis B or C serology: hepatitis B surface antigen (HBsAg+), antibodies against hepatitis B core antigen (anti-HBc+), antibodies against hepatitis C virus (anti-HCV+) at screening. Note: Patients with anti-HBc+ only and negative hepatitis B virus- deoxyribonucleic acid as well as patients with anti-HCV+ only and negative HCV-ribonucleic acid may be included.
• Primary Sclerosing Cholangitis,
• Wilson*s Disease,
• Hemochromatosis
• Definite autoimmune hepatitis or overlap syndrome,
• Nonalcoholic steatohepatitis (NASH),
• Alcoholic steatohepatitis (ASH),
• Cholangiocarcinoma,
• Drug-induced liver disease,
• Suspected or proven liver cancer,
2. Treatment with any of the following drugs within the last 4 weeks prior to

screening: any glucocorticosteroids, azathioprine or other immunosuppressive drugs (e.g., cyclophosphamide, cyclosporine, methotrexate, tacrolimus, 6-mercaptopurine, colchicine), pentoxyfylline, biologics (e.g., anti-tumor necrosis factor-* therapy),
NOTE: Treatment with dermal, inhalative, or nasal topical glucocorticosteroids for up to 10 days within the last 4 weeks prior to screening or as planned concomitant treatment for up to 10 days/4 weeks is allowed.
3. Treatment with farnesoid X receptor-agonists within the last 8 weeks prior to screening,
4. Starting treatment with fibrates within the last 8 weeks prior to screening,
5. Liver cirrhosis. NOTE: Patients with compensated cirrhosis and a Child-Pugh Score <8 are allowed to participate,
6. History or presence of hepatic decompensation (e.g., variceal bleeding, international normalised ratio [INR] > 1.3), hepatic encephalopathy or poorly controlled ascites (serum albumin less than 3.2 g/dl),
7. Total bilirubin > 2x ULN at screening visit, unless due to Gilbert*s syndrome,
8. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5x ULN at screening visit,
9. Any known relevant infectious disease (e.g., active tuberculosis, acquired immunodeficiency syndrome [AIDS]-defining diseases),
10. Abnormal renal function (glomerular filtration rate estimated from cystatin C
< 30 ml/min) at screening visit,
11. Thyroid-stimulating hormone (TSH) > ULN at screening (elevated levels [4.2-10 µU/mL] are acceptable if fT4 is measured and within the normal range),
12. Current history of significant alcohol consumption (> 30 g/d in men, > 20 g/d in women on average) for a period of more than 3 consecutive months within 1 year prior to screening,
13. Inability to reliably quantify alcohol consumption as judged by the investigator,
14. Any illness or medical conditions that are unstable or could jeopardize the safety of the patient or his/her compliance in the trial or might interfere with the interpretability of the trial results,
15. Previous or concurrent cancer except cervical carcinoma in situ, treated basal cell carcinoma, or any cancer curatively treated < 3 years before screening,
16. Known intolerance/hypersensitivity to the Investigational Medicinal Product (IMP) or its excipients, or to drugs of similar chemical structure or pharmacological profile,
17. Well-founded doubt about the patient*s cooperation, e.g., because of addiction to alcohol or drugs,
18. Existing or intended pregnancy or breast-feeding,
19. Participation in another clinical trial and having received investigational medicinal product (IMP) within the last 30 days or <= 5 terminal elimination half-lives of previous IMP, whichever is longer, prior to screening visit, simultaneous participation in another clinical trial, or previous participation

in this trial and having received IMP,
20. Dependency (as an employee or relative) on the sponsor or investigator,
21. Commitment to an institution by virtue of an order issued either by the judicial or the administrative authorities,
22. Legal incapacity or limited legal capacity.

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):	29-11-2022
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	norucholic acid

Ethics review

Approved WMO

Date:	16-05-2022
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2024
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	EUCTR2021-001431-56-NL
CCMO	NL79915.018.22
Other	www.clinicaltrialsregister.eu