Double-blind, randomized, placebo-controlled, phase III study comparing norursodeoxycholic acid capsules with placebo in the treatment of primary sclerosing cholangitis

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This study has been transitioned to CTIS with ID 2023-510200-42-00 check the CTIS register for the current data. Primary:• To show the superiority of norursodeoxycholic acid (norUDCA) compared to placebo in the treatment of Primary Sclerosing...

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

Summary

ID

NL-OMON54551

Source
ToetsingOnline

Brief title
NUC-5/PSC

Condition

- Hepatic and hepatobiliary disorders

Synonym
Primary Sclerosing Cholangitis (PSC)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: norUDCA, PSC

Outcome measures

Primary outcome

Partial normalization of s-ALP to < 1.5x ULN and no worsening of disease stage as determined by the Ludwig stage at the week 96 visit compared to baseline.

The primary endpoint consists of two criteria:

1) s-ALP criterion: yes = if s-ALP < 1.5x ULN at week 96 (partial normalization), no = if s-ALP >= 1.5x ULN at week 96. If no value at week 96 exists, the s-ALP criterion is *no*.

2) Histological criterion: yes = no worsening of the Ludwig stage; no = otherwise or if no Ludwig stage is available at week 96.

The primary endpoint is:

- Yes = if both criteria above are *yes*.
- No = otherwise.

Secondary outcome

Key secondary efficacy endpoint:

• Partial normalization of s-ALP to < 1.5x ULN and no worsening of disease stage as determined by the modified Nakanuma score at the week 96 visit compared to baseline (derivation according to primary efficacy endpoint)

Other secondary efficacy endpoints:

• Change in liver stiffness <= 1.3 kPa/year at the week 96 visit (last observation carried forward [LOCF]) compared to baseline,

• No worsening of disease stage according to Ludwig staging compared to baseline.

• No worsening of disease stage according to modified Nakanuma score compared to baseline.

• No worsening of disease stage according to PSC histoscore compared to baseline

• No worsening of disease stage according to Ishak staging compared to baseline.

• Improvement of histological grading according to Ishak by at least 1 point.

• Partial normalization of s-ALP (< 1.5x ULN) at the week 96 visit,

• At least 40% reduction in s-ALP between baseline and the week 96 visit (LOCF),

• Course of Enhanced Liver Fibrosis (ELF) test,

• No worsening of liver histology assessed by morphometric measurement,

• Course of interleukin 8 between baseline and the week 96 visit (LOCF),

• Hannover Score for survival in PSC at the week 96 visit (LOCF) compared to Hannover Score at baseline,

• Normalization of s-ALP (< ULN) at the week 96 visit,

• s-ALP at each study visit (screening to EOT DBE),

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

EOT DB, and from EOT DB to the last visit of the DBE phase,

• Dominant strictures,

• Need for treatment of dominant strictures (e.g., stenting or dilatation),

• Gamma-glutamyltransferase (γ-GT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamate dehydrogenase (GLDH), and serum bilirubin levels at each study visit (screening to the last visit of the DBE phase),

• Absolute and relative changes (%) of γ-GT, AST, ALT, GLDH, and serum bilirubin from baseline to each visit up to EOT DB, and from EOT DB to the last visit of the DBE phase,

• Absolute change in the score for pruritus (measured by VAS) from baseline to EOT DB, and from EOT DB to the last visit of the DBE phase,

• Absolute change in the score for fatigue (measured by adapted PBC-40 questionnaire) from baseline to EOT DB, and from EOT DB to the last visit of the DBE phase,

• One or more clinical events (CCC or HCC or CRC or transplantation or death or cirrhosis-related events) at any time during the DB phase.

Study description

Background summary

Primary Sclerosing Cholangitis (PSC) is a slowly progressing chronic cholestatic liver disease of assumed autoimmune, but finally unidentified etiology, characterized by a chronic inflammatory and fibro-obliterative destruction of extra-, and intrahepatic bile ducts. PSC is a progressive disease characterized by diffuse inflammation, fibrosis, and strictures of the intra- and/or extrahepatic bile ducts with an impaired biliary secretion of potentially aggressive bile fluid, finally leading to Biliary Cirrhosis in almost all patients. The lack of effective medical treatment for PSC is

reflected by a frequent need for liver transplantation, which currently represents the only life-extending therapeutic option. In addition, PSC patients are at highly increased risk to develop cholangiocarcinoma and other cancers. Prognosis for PSC patients varies greatly but generally is poor with an estimated 10-year survival of approximately 65%. A population-based study estimated 21.3 years as the median time from diagnosis to the need of liver transplantation or liver-related death in the entire cohort and 13.2 years in a combined transplant centers cohort.

The majority of cases (approx. 70%) occur in association with Inflammatory Bowel Disease (IBD, i.e., mainly with Ulcerative Colitis). Twice as many men as women are affected, and PSC is diagnosed most frequently between 25 and 40 years of age. PSC is found with a prevalence of approximately 10/100,000 in Northern Europe populations. At presentation, approximately 15-55% of PSC patients are asymptomatic, but patients are at increased risk for developing symptoms over time. Fatigue, pruritus, jaundice, and abdominal discomfort develop in 60% of the cases.

The biochemical hallmark of PSC is a cholestasis with an elevation in serum Alkaline Phosphatase (s-ALP) level. Increases between 3-10 times the upper limit of normal occur in 95% of cases. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are usually 2-3 fold higher than normal. Patients with PSC often have fluctuations in bilirubin and s-ALP levels during the course of the disease. Periods of clinical and cholestatic relapses follow periods of clinical remission with fewer symptoms of cholestasis.

Although PSC is a rare disease it portends a considerable healthcare burden: It affects young patients, there is no effective medical therapy, and PSC is associated with a high rate of complications. The list of medical therapies tested negative for PSC is long, comprising azathioprine, cyclosporine, methotrexate, infliximab and others.

Study objective

This study has been transitioned to CTIS with ID 2023-510200-42-00 check the CTIS register for the current data.

Primary:
• To show the superiority of norursodeoxycholic acid (norUDCA) compared to placebo in the treatment of Primary Sclerosing Cholangitis (PSC) with regard to prevention of disease progression assessed by liver histology and by partial normalization of serum Alkaline Phosphatase (s-ALP) levels in patients with PSC.
Secondary:
• To study safety and tolerability (Adverse Events, laboratory parameters) of norUDCA,
• To assess quality of life.

Study design

This is a double-blind, randomized, multi-center, placebo-controlled, comparative, phase III trial. The study will be conducted with two treatment groups in the form of a parallel group comparison and will serve to compare oral treatment with either 1500 mg/d norursodeoxycholic acid capsules or placebo capsules for the treatment of Primary Sclerosing Cholangitis.

Double-blind (DB), randomized (2:1) treatment phase:
Patients will be randomized to receive a 96 week, double-blind treatment with:
Group A: Norursodeoxycholic acid once daily (OD)
Week 1 + 2: 2x250 mg capsules = 500 mg OD
Week 3 + 4: 4x250 mg capsules = 1000 mg OD
Week 5 - 96: 6x250 mg capsules = 1500 mg OD
Group B: Placebo capsules for norursodeoxycholic acid OD
Week 1 + 2: 2x placebo capsules
Week 3 + 4: 4x placebo capsules
Week 5 - 96:6x placebo capsules
Blinding is achieved by the application of visually identical capsules (verum and/or placebo) to each patient.

Double-blind extension (DBE) phase: Week 97 until up to week 192.
Patients will receive the same double-blind treatment as in the DB-phase with:
Group A: Norursodeoxycholic acid 1500 mg OD
6x250 mg capsules
Group B: Placebo capsules for norursodeoxycholic acid OD
6x placebo capsules

Open-label extension (OLE) phase: week 192 until up to week 288.
All patients will receive verum (Norursodeoxycholic acid 1500 mg OD, 6x250 mg capsules)

Intervention

One group is receiving once daily 1500 mg norursorsodeoxycholic acid (= 6 capsules) and the other group is receiving once daily a placebo (= 6 capsules).
OLE phase: All patients will receive Norursodeoxycholic acid 1500 mg OD, 6x250 mg capsules.

Study burden and risks

NorUDCA is intended for the treatment of PSC. In patients with PSC there is a high incidence of cholangiocarcinoma and an elevated risk of developing colon cancer and no medical therapy has been proven successful in slowing the disease progression. NorUDCA has been shown to markedly improve biochemical and histological features in a mouse model of sclerosing cholangitis without toxic

effects. The no observed adverse effect level (NOAEL) for chronic toxicity in rats after treatment with norUDCA over 26 weeks was 300 mg/kg/day; the NOAEL in minipigs after treatment with norUDCA over 39 weeks was 2000 mg/kg/day (for details see Investigator*s Brochure). Treatment of rats over 90 days with the combination of norUDCA and UDCA at drug ratios of 2:1 and 1:1, which is the expected range of drug ratios in this clinical trial, was well tolerated with a NOAEL of 750 norUDCA mg/kg/day (+ 375 or 750 UDCA mg/kg/day, respectively). Considering the planned dose to be used, there appears to be an adequate safety margin for administration of the compound to patients with active PSC in a phase III trial. In addition, the results of two phase I clinical trials (NUC-1/BIO, NUC-2/BIO) and a phase II clinical trial (NUC-3/PSC) indicated an advantageous benefit/risk ratio.
Diagnostic procedures and examinations exercised in this clinical trial are mostly routine or non-invasive procedures. Only at screening and both end of treatment visits, liver biopsies will be taken for histological assessment. The histological grading will serve to increase the evidence of the trial and to confirm the prognostic validity of other efficacy endpoints which are based on non-invasive techniques like liver stiffness measured by elastography or decrease in s-ALP. Therefore, a potential risk associated with liver biopsy sampling seems to be justified with regard to the increased significance of the primary efficacy endpoint of the trial.
A treatment duration of 2 x 96 weeks was chosen to investigate long-term effects of norUDCA treatment on efficacy endpoints and safety variables. Regular control visits and an increased visit frequency at the beginning of the first treatment phase will serve to detect any untoward effects as early as possible.
For the time being no standard therapy is available. UDCA has been used off-label, but was associated with a high rate of Serious Adverse Events and did not improve survival when used at a high dose. Therefore, it seems justified to introduce a placebo arm in this clinical study. Furthermore, patients already receiving UDCA will be allowed to continue this medication.
To detect any potential additive adverse effects of concomitant UDCA and norUDCA treatment at the earliest possible time point, the study treatment will start with a low dose of norUDCA (500 mg OD) which will be escalated over several weeks until the full dose of 1500 mg OD will be reached from treatment week 5 onwards. Furthermore, there will be an increased visit frequency of every two weeks during the first two months of the first treatment phase, concomitant UDCA treatment will be limited to a maximum daily dose of 20 mg/kg body weight/day, and a data and safety monitoring board will be established.

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. Signed Informed Consent
2. Males or Females
3. Verified PSC
4. Liver Biopsy available
8. Women of child-bearing potential who are sexually active have to apply a highly effective method of brith control

For open-label extension (OLE) phase:
1. Signed Informed Consent
2. DBE phase completed with Visit 22

Exclusion criteria

1. History or presence of other concomitant liver diseases
4. Secondary causes of Sclerosing Cholangitis
11. Total bilirubin > 4.0 mg/dl (>68 µmol/L) at screening or baseline
13. Any relevant infectious disease (e.g. AIDS)

14. Abnormal renal function
15. 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)
17. Any active malignant disease
18. Known intolerance/hypersensitivity to study drug, or drugs of similar chemical structure or pharmacological profile
19. Well-founded doubt about the patient's cooperation
20. Existing or intented pregnancy or breast-feeding
21. Participation in another clinical trial within the last 30 days

Study design

Design

Study phase:	3
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):	14-05-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	-
Generic name:	norursodeoxycholic acid or Norucholic acid

Ethics review

Approved WMO Date:	06-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-12-2022

Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	25-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	10-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	14-02-2023
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Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	28-03-2024
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Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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Date:	04-06-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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
EU-CTR	CTIS2023-510200-42-00
EudraCT	EUCTR2016-003367-19-NL
CCMO	NL64449.018.18