Double-blind, randomised, placebo-controlled, multi-centre phase III clinical study comparing the combination of ursodeoxycholic acid capsules plus budesonide capsules to ursodeoxycholic acid capsules plus placebo in the treatment of primary biliary cirrhosis

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To compare the efficacy and tolerability of a combination therapy with ursodeoxycholic acid (12-16 mg/kg body weight plus budesonide (9mg/d) vs. ursodeoxycholic acid (12-16 mg/kg BW/d) plus placebo in the treatment of PBC. To study safety and...

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

Summary

ID

NL-OMON33623

Source
ToetsingOnline

Brief title
Ursodeoxycholic acid plus budesonide vs. ursodeoxycholic acid alone in PBC

Condition

- Hepatic and hepatobiliary disorders

Synonym
inflammation of the bile ducts of the liver, Primary Biliary Cirrhosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Budesonide, Patients, Primary Biliary Cirrhosis, Ursodeoxycholic acid (UDCA)

Outcome measures

Primary outcome

Rate of patients without treatment failure after 3 years of treatment.

Treatment failure is defined as:

- death, or

- registration on the liver transplant waiting list, or

- cirrhosis defined by histology (staging according to Ludwig), or

- presence of esophageal varices and/or ascites

Secondary outcome

- Normalisation of serum levels of AP

- Improvement of serum levels of AP and bilirubin

- Serum bilirubin levels more than 50 *mol/L (3.0 mg/dl), or

Fall in serum albumin count of 10% and to a value of less than 34 g/L

- Course of pruritus (measured by VAS)

- Course of fatigue (measured by PBC-40)

- Course of Mayo Risk Score

- Assessment of inflammatory activity2,3

- Quality of Life by PBC-40

- Global assessment of efficacy by patient and investigator

- Fall in platelet counts to < 135.000/mm³

- Fall in the prothrombin ratio of more than 25% and to a value of < 70%

- Fibrosis marker (hyaluronic acid)

- Doubling in the serum concentration of hyaluronic acid to more than 80 *g/L

or increase to a value of more than 100*g/L

Study description

Background summary

Right now the monotherapy with UDCA is the only approved therapy for PBC. The therapy is most effective, if started at early stages of the disease. Budesonide, a topical acting corticosteroid, seems a suitable add on therapy for UDCA. The safety of budesonide in the tratment of Crohn*s Disease, an inflammation of the duodenal wall, is well demonstrated. Furthermore, budesonide is used in the treatment of several diseases of the liver. Until now only two studies have been performed evaluating the combination of budesonide and UDCA in the treatment of PBC. Both of these studies showed a superiority in the combinational treatment compared to the UDCA-monotherapy and budesonide was well tolerated.

Study objective

To compare the efficacy and tolerability of a combination therapy with ursodeoxycholic acid (12-16 mg/kg body weight plus budesonide (9mg/d) vs. ursodeoxycholic acid (12-16 mg/kg BW/d) plus placebo in the treatment of PBC. To study safety and tolerability in the form of adverse events and laboratory parameters. To assess patients Quality of Life.

Study design

This is a double-blind, randomised, placebo-controlled, multi-centre, comparative, phase III clinical trial carried out with 183 patients.

Intervention

Patients with treatment of UDCA (budesonide or UDCA alone for 36 months.

Study burden and risks

11 visits at the hospital, 9 x physical examinations, 11 x vital signs, 11 x blood withdrawal (total 225 mL blood) for security/serology/fibrosis marker (hyaluronic acid)/bone metabolism, 11 x urine sample, 2 x liver biopsies, 2 x FibroScan (optional), 3 x bone density measurement, 4 x course of pruritus, 4 x questionnaires (fatigue, quality of life), treatment with budesonide/UDCA or UDCA alone for 36 months, 1 diary for medication/adverse events (only has to be filled in in case deviations from regular intake/adverse events/concomitant medications) for 36 months.
The used medications are all registered in the Netherlands, their safety is determined. The removal of liver biopsies is of low risk. However, in few cases complications might arise. Blood withdrawal can cause discomfort e.g. bruises, inflammation at the injection site etc.

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. Age > 18 years
3. UDCA treatment for at least 6 months prior to inclusion
4. Liver biopsy compatible with PBC
5. Liver biopsy performed within the last 6 months prior to inclusion
6. PBC patients at risk of disease progression based on one or more of the following criteria:
- serum alkaline phosphatase * 3 times the upper limit of normal (corresponding to 312 U/L for women and 387 U/L for men) at any time since diagnosis of PBC
or
- ALT or AST * 2 times upper limit of normal (corresponding to 70 U/L for women and 100 U/L for men) at inclusion or
- Total Bilirubin * 1.0 mg/dL or
- Moderate to severe periportal or periseptal lymphocytic interface hepatitis or
- periportal and portal fibrosis with numerous septa (Ludwig stage III) without cirrhosis
7. Type 2 anti-mitochondrial antibodies > 1:40 by indirect immunofluorescence
8. Women of child-bearing potential have to apply appropriate contraceptive methods, e.g., hormonal contraception, intrauterine device (IUD), doublebarrier method of contraception (e.g., use of a condom and spermicide),
partner has undergone vasectomy and subject is in monogamous relationship.
The investigator is responsible for determining whether the subject has adequate birth control for study participation.

Exclusion criteria

1. Histologically proven cirrhosis
2. Positive Hepatitis B or C serology
3. Positive HIV serology
4. Primary Sclerosing Cholangitis
5. Wilson*s Disease
6. Celiac Disease (if not controlled)
7. alpha1-anti-Trypsin-deficiency
8. Haematochromatosis
9. Autoimmune-Hepatitis
10. Treatment with corticosteroids (except inhalative corticosteroids) within the last 2 months prior to inclusion and/or treatment with any of the following drugs
within the last 3 months prior to inclusion: colchicine, azathioprine or other immunosuppressive drugs, chlorambucil, D-penicillamine, fibrates, or antihyperlipidemic drugs.
11. Treatment with ketoconazole or other CYP3A inhibitors within the last 4 weeks

before baseline; rifampicin (up to 600 mg/d) is allowed to treat pruritus until baseline
12. Sonographic or endoscopic signs of portal hypertension
13. Ascites or history of ascites
14. Hepatic encephalopathy or history of hepatic encephalopathy
15. Total bilirubin > 3.0 mg/dl
16. Albumin < 36 g/L
17. Prothrombin time < 70%
18. Platelet count < 135.000/mm3
19. Osteoporosis proven by bone densitometry
20. Diabetes mellitus (defined as B-Glucose > 125 mg/dl on an empty stomach), even when controlled
21. Hypertension, defined as persistent raised blood pressure > 140/90 mmHg
22. Suspected non-compliance of the patient (suspected difficulties to comply with the study period of 36 months)
23. Severe co-morbidity substantially reducing life expectancy
24. Known intolerance/hypersensitivity/resistance to study drugs or drugs of similar chemical structure or pharmacological profile
25. Existing or intended pregnancy or breast-feeding
26. Participation in another clinical trial within the last 30 days, simultaneous participation in another clinical trial, or previous participation in this trial

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:	Recruitment stopped
Start date (anticipated):	01-06-2009
Enrollment:	6

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Budenofalk 3 mg capsules
Generic name:	budesonide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Ursofalk 250 mg capsules
Generic name:	ursodeoxycholic acid
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2015
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	EUCTR2007-004040-70-NL
CCMO	NL22490.018.08