Double-blind, randomized, placebo-controlled, phase II dose-finding study comparing different doses of Rhudex granules with placebo in the treatment of primary biliary cholangitis

Published: 08-10-2020
Last updated: 17-01-2025

Primary:To evaluate the efficacy of 3 doses of RhuDex vs placebo for the treatment of PBC in patients with an inadequate response to UDCA.Secondary:• To identify efficacious RhuDex dose(s) for the treatment of PBC for further evaluation in phase III...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gallbladder disorders
Study type	Interventional

Summary

ID

NL-OMON55327

Source
ToetsingOnline

Brief title
RHUBY: RHUdex in primary BiliarY cholangitis

Condition

- Gallbladder disorders

Synonym
cholangitis, inflamnation in bile duct

Research involving

Human

Sponsors and support

Primary sponsor: AML Clinical Services BV
Source(s) of monetary or material Support: dr. Falk Pharma GmbH

Intervention

Keyword: cholangitis, Primary bilary cholangitis (PBC)

Outcome measures

Primary outcome

Relative change (%) in ALP from baseline to EOT.

Secondary outcome

• Proportion of patients with at least 10%, 20%, and 40% reduction in ALP between baseline and EOT,

• Proportion of patients with normalisation of ALP (< ULN) at least at one post-baseline visit up to EOT,

• Proportion of patients with partial normalisation of ALP (< 1.5x ULN) at least at one post-baseline visit up to EOT,

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

• Absolute and relative changes (%) of ALP from baseline to each visit up to EOT, and from EOT to the follow-up visit,

• Gamma-glutamyltransferase (γ-GT), AST, ALT, and total and conjugated bilirubin levels at each trial visit (screening to follow-up),

• Absolute and relative changes (%) of γ-GT, AST, ALT and total and conjugated bilirubin levels from baseline to each visit up to EOT, and from EOT to the follow-up visit.

Study description

Background summary

This double-blind, randomised, multi-centre, placebo-controlled, comparative phase II trial will compare oral treatment with 50, 100 or 200 mg/day RhuDex granules vs placebo granules for the treatment of PBC.
Previous phase I trials evaluated the safety and PK of different formulations of RhuDex in healthy volunteers. To date only one study was performed in patients (indication RA). The planned trial is expected to provide efficacy and safety data for RhuDex granules in patients with PBC.
The tested dosing regimen was found to be safe and established a systemic exposure (plasma concentration) in the range of the in vitro doses with relevant pharmacodynamic effects. The PK profile of RhuDex is characterised by accumulation in the hepatobiliary system providing a natural targeting for PBC.
Efficacy data will include biochemical and symptomatic endpoints. Furthermore, the planned trial should provide additional information on a safe and effective dose from 25 to 100 mg RhuDex BID 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 RhuDex is expected to be also seen within 12 weeks.
The patients will be followed up until 4 weeks after the last dose of the investigational medicinal product (IMP), which is much longer than 5 times the half-life of RhuDex (about 120 hours).
As all patients will continue standard of care treatment with UDCA, a placebo arm will be included as control due to regulatory recommendations to evaluate dose-related benefits and adverse effects in randomised, double-blind, placebo controlled studies.
Based on the results obtained in this trial, the optimal dose with regard to clinical outcomes might be evaluated further in a phase III confirmative trial.

Study objective

Primary:
To evaluate the efficacy of 3 doses of RhuDex vs placebo for the treatment of PBC in patients with an inadequate response to UDCA.
Secondary:
• To identify efficacious RhuDex dose(s) for the treatment of PBC for further evaluation in phase III,
• To study safety and tolerability of RhuDex.

Study design

This is a double-blind, randomised, multi-centre, placebo-controlled,

comparative, exploratory phase II dose-finding trial. The trial will be conducted with 4 treatment groups in the form of a parallel group comparison and will serve to compare oral treatment with either 50, 100 or 200 mg/day RhuDex gastro-resistant granules vs placebo granules for the treatment of PBC.
The up to 4-week screening and randomization period will be followed by a 12-week double-blind treatment period and a 4-week follow-up period.
The trial will be performed according to a 2-stage group-sequential adaptive design with one planned interim analysis.
Double-blind, randomised (1:1:1:1) treatment phase:
Patients will be randomised to receive a 12-week, double-blind treatment with:
Group A: RhuDex 25 mg (31.75 mg RhuDex choline salt) twice daily (BID)
1 sachet with a blend of 750 mg RhuDex granules and 2,250 mg placebo granules
Group B: RhuDex 50 mg (63.5 mg RhuDex choline salt) BID
1 sachet with a blend of 1500 mg RhuDex granules and 1,500 mg placebo granules
Group C: RhuDex 100 mg (127 mg RhuDex choline salt) BID
1 sachet with 3,000 mg RhuDex granules
Group D: Placebo granules for RhuDex BID
1 sachet with 3,000 mg placebo granules
Follow-up phase: Until 4 weeks after the patient*s individual end of treatment.
Blinding is achieved by the application of the same amount of granules for each verum dose and placebo to each patient. Placebo granules match verum granules in size, taste and appearance; the granules of both verum and placebo are filled in identical sachets.
All patients will continue their pre-trial dose of UDCA throughout trial participation without changing the dosing regimen.

Intervention

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Group C: RhuDex 100 mg (127 mg RhuDex choline salt) BID
1 sachet with 3,000 mg RhuDex granules
Group D: Placebo granules for RhuDex BID
1 sachet with 3,000 mg placebo granules

Study burden and risks

Treatment with RhuDex can lead to undesirable effects or discomforts.

These side effects are common (occurs in 1 in 10 people or more):
- Headache,
- Blurred vision,

- Diarrhoea, frequent bowel movements, vomiting, nausea,
- Common cold (nasopharyngitis),
- Decreased appetite,
- Dizziness,
- Cough,
- Hot flush,

These side effects occur, but not often:
- Rapid heartbeat (palpitations),
- Irritation and redness of the membrane covering the eye (conjunctivitis), dry eye, visual impairment,
- Upper abdominal pain, abdominal pain, constipation, dyspepsia, gas/upset stomach, lip pain,
- Chest discomfort, influenza like illness, fatigue,
- Inflammation of stomach and intestine (viral gastroenteritis), oral herpes, upper respiratory tract infection, shingles (herpes zoster),
- Alanine aminotransferase (liver value) increased, abnormal heart activity (electrocardiogram QT corrected interval prolonged), hepatic enzymes increased, liver function test abnormal,
- High blood sugar (hyperglycemia),
- Musculoskeletal pain,
- Sleepiness (somnolence),
- Difficulty breathing (dyspnoea), throat/upper neck (pharyngolaryngeal) pain,
- Increased sweating (hyperhidrodis),
- Flushing, inflammation of a vein (phlebitis).

RhuDex may also cause side effects that are unknown.

Tests
The study-related tests may be associated with risks or lead to discomforts:
• Blood sampling: This might cause discomfort, bruising or, unusually, clotting of the vein at the site where the needle is inserted. In rare cases, it might cause venous inflammation (thrombophlebitis) or nerve injury.
At each visit, approx. 30 ml blood will be sampled. In total, approx. 150 ml blood will be sampled in the course of the study. This amount should not cause any problems in adults. In comparison: at the blood bank, 500 mL of blood is collected at one time
• Electrocardiogram (ECG): You will be asked to lie flat on a table, and several small electrode pads (like stickers) will be placed on the body which may cause some transient redness or itching.
• Ultrasound: This application requires use of a lubricant jelly to enhance transmission of the sound waves. The procedure is non-invasive and poses no relevant known risks to you other than a gentle pressure. Please let your physician know about possible allergies to the contact jelly.
• Fibroscan (only if available at your study site): This technology is similar to an ultrasound device. It is non-invasive and poses no relevant known risks to you other than a gentle pressure. Please let your physician know about

possible allergies to the contact jelly.

Subjects have to visit the clinic more frequent (6 times in 16 weeks) then standard of care (once per year).

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

Patients who meet all of the following criteria can be enrolled into the trial:
1. Patient is able to understand the information on the trial and has signed the informed consent form,
2. Male or female patients >= 18 and < 75 years,
3. PBC verified by at least 2 out of the following 3 criteria (consistent with EASL practice guidelines [2017]) :

• Chronic cholestatic disease (e.g. elevated serum ALP) of at least 6 months duration,
• Positive AMA titer or presence of PBC-specific antibodies,
• Liver biopsy compatible with the diagnosis of non-cirrhotic PBC,
4. UDCA treatment for at least 6 months (with a stable dose for >= 3 months of at least 12 mg/kg/day) prior to baseline,and no foreseen changes of the dosing regimen throughout trial participation,
5. Inadequate response to UDCA treatment defined by serum ALP levels between 1.5x and 10x the upper limit of normal (ULN) at screening,
6. Women of childbearing potential agree to use during the entire duration of the trial and until 4 weeks following the last dose of trial treatment a highly effective method of birth control, 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 (IUDs), sexual abstinence, or vasectomised partner. Women of non-childbearing potential (surgically sterile [e.g. hysterectomy, bilateral salpingectomy, bilateral oophorectomy], or postmenopausal with at least 2 years without spontaneous menses) may be included. The investigator is responsible for determining whether the patient uses adequate birth control for trial participation

Exclusion criteria

Patients who meet one or more of the following criteria are not allowed to be enrolled into the trial:
1. History or presence of other relevant concomitant liver diseases including:
• 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+),
Note: Patients with anti-HBc+ only and negative hepatitis B virus (HBV)-deoxyribonucleic acid (DNA) as well as patients with anti-HCV+ only and negative HCV-ribonucleic acid (RNA) may be included
Primary Sclerosing Cholangitis,
• Wilson*s Disease,
• Haemochromatosis,
• Current histologic and serologic evidence to support a clinical diagnosis of concomitant autoimmune hepatitis requiring treatment,
• 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) orpentoxyfylline,
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 and biologics (e.g. anti-TNF-α therapy) within the last 8 weeks prior to screening,
4. Treatment with fibrates unless on stable dose for 8 weeks prior to screening and no foreseen changes of the dosing regimen throughout trial participation,
5. Liver cirrhosis confirmed by an accepted diagnostic procedure (e.g. histology, fibrosis-4 [FIB-4] score > 4.03, fibroscan >= 16.9 kPa),
6. History or presence of hepatic decompensation (e.g. variceal bleeding hepatic encephalopathy or poorly controlled ascites),
7. Serum albumin less than 3.2 g/dL, at screening,
8. Total bilirubin > 2x ULN, at screening,
9. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5x ULN at screening visit,
10. History of stroke or coronary artery disease,
11. History of sudden death or cardiovascular death before the age of 50 in any first degree relative,
12. History or family history of hereditary clotting disorder,
13. Any known relevant infectious disease (e.g. active tuberculosis, acquired immunodeficiency syndrome-defining diseases),
14. Abnormal renal function (glomerular filtration rate estimated from cystatin C < 60 mL/min) at screening visit,
15. Thyroid-stimulating hormone > ULN at screening (elevated levels [4.2-10 µU/mL] are acceptable if free thyroxine 4 is measured and within the normal range),
16. Current history of significant alcohol consumption (> 30 g/day in men, > 20 g/day in women on average) for a period of more than 3 consecutive months within 1 year prior to screening,
17. Inability to reliably quantify alcohol consumption as judged by the investigator,
18. Any illness or medical conditions that are unstable or could jeopardise the safety of the patient and his/her compliance in the trial or might interfere with the trial results,
19. Previous and concurrent HIV infection,
20. Previous or concurrent cancer except cervical carcinoma in situ, treated basal cell carcinoma, or any cancer curatively treated < 3 years before trial entry,
21. Known intolerance/hypersensitivity to the Investigational Medicinal Product (IMP) or its excipients, or to drugs of similar chemical structure or pharmacological profile,
22. Well-founded doubt about the patient*s cooperation, e.g. because of addiction to alcohol or drugs,
23. Existing or intended pregnancy or breast-feeding,
24. Participation in another clinical trial and having received 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,
25. Dependency (as an employee or relative) on the sponsor or investigator,
26. Commitment to an institution by virtue of an order issued either by the judicial or the administrative authorities,
27. 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:	Completed
Start date (anticipated):	21-06-2021
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rhudex
Generic name:	Rhudex

Ethics review

Approved WMO

Date:	08-10-2020
Application type:	First submission

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-12-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2020-001961-34-NL
CCMO	NL74708.056.20
Other	see J

Study results

Date completed:	08-03-2023
Results posted:	24-11-2023

Summary results
Trial ended prematurely

First publication
17-11-2023