An adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study to investigate the efficacy and safety of LNP023 in primary IgA nephropathy patients

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To evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment in patients with IgA nephropathy.

Ethical review	Approved WMO
Status	Completed
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON50202

Source
ToetsingOnline

Brief title
CLNP023X2203

Condition

- Nephropathies

Synonym
IgA kidney disease, IgAN

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V. (sponsor/verrichter van dit onderzoek)

Intervention

Keyword: chronic kidney disease, IgA nephropathy, LNP023, proteinuria

Outcome measures

Primary outcome

To evaluate the dose response relationship of LNP023 on the reduction in

proteinuria versus placebo after 90 days of treatment in patients with IgA

nephropathy.

Secondary outcome

- To evaluate the safety and tolerability of LNP023

- To assess the effect of LNP023 on renal function up to 90 days of treatment

(combining Part 1 and Part 2 of the study)

- To assess the pharmacokinetics of LNP023

- To assess the effect of LNP023 on alternative complement pathway

- To estimate the lowest dose that provides maximal reduction of proteinuria

- To assess the effect of LNP023 on renal function up to Day 180 (Part 2 of the

study)

Study description

Background summary

Antibodies belong to the body's immune system. The immune system must protect the body against organisms that can enter the body, such as bacteria, viruses.

If the immune system recognizes a foreign substance (eg a bacterium), it will form antibodies against this substance. This happens to defend the body.

In IgA kidney disease, IgA (immunoglobulin A) antibodies also end up in the kidneys. This caused an inflammatory reaction in the kidney filters. This leads among other things to the loss of protein via the urine.

If an important part of the body's immune system becomes too active, diseases can arise such IgA nephropathy. LNP023 inhibits the functioning of this part of the immune system. As a result, the disease can become less active and the symptoms can become less serious. For example, the amount of protein that disappears from the body

LNP023 has not yet been approved ("registered") by the Dutch government as a medicine. Doctors are not yet allowed to prescribe the drug. Registration with patients is required for registration. So far, approximately 78 healthy subjects have been treated with LNP023 in a study.

Study objective

To evaluate the dose response relationship of LNP023 on the reduction in proteinuria versus placebo after 90 days of treatment in patients with IgA nephropathy.

Study design

This is an adaptive seamless randomized, double-blind, placebo-controlled, dose ranging study evaluating the efficacy and safety LNP023 following 90 - 180 days of treatment. In Part 1, 4 groups of IgAN patients will be randomized to three doses (10mg, 50mg and 200mg b.i.d) of LNP023 or Placebo. At the end of Part 1, a pre-specified interim analysis will be performed to evaluate the initial response to therapy and to make design choices for Part 2 using predefined rules. The trial may either be stopped for futility, or continued with some design adaptations (increase of the sample size and addition of a dose arm of either 25 mg or 100 mg b.i.d) for the treatment phase of Part 2. Hence, patients in Part 2 will be randomized to placebo, 10 mg, 50 mg, 200 mg b.i.d and a 4th active dose of either 25 mg b.i.d or 100 mg b.i.d. 100 mg dose was chosen by the DMC after the interim analysis Part 1. The treatment phase will be extended to 180 days in Part 2 compared to Part 1, during which additional efficacy and safety data will be collected. Data from Part 1 and Part 2 of the study up to approximately Day 90 will be pooled and used for the interim analysis Part 2 (IA2).

Intervention

LNP023 is available as 5 mg, 25 mg, 100 mg and matching placebo capsules.

b.i.d. Patients will be randomized to either 0 mg (matching Placebo), 10mg, 50mg, or 200 mg b.i.d. in Part 1. Either the dose of 25 mg or 100 mg b.i.d will be added in Part 2 based on the interim analysis results in Part 1. 100 mg was chosen by DMC after interim analysis part 1.

Study burden and risks

Part 1 of the study takes 7 to 9 months. Part 2 takes 10 to 12 months. The study starts with the screening visit and a start-up phase of 1 to 3 months. Then there is a treatment period of about 3 months in Part 1 and 6 months in Part 2 during which you use the study medication. Three months after the last administration of the study medication, there is a final check for the study.

Based on 10-12 visits, the burden will be as follows:
- Physical examination: 6x in Part 1, 8x in Part 2
- ECG: 10x in Part 1, 11x in Part 2
- Vital signs: 14x
- Blood test: 20x (max 350 ml in total for 9 months in Part 1 and 450ml in total for 12 months in Part 2)
- Pregnancy test (if applicable): 6x in Part 1, 7x in Part 2
- Urine test: 10x in Part 1, 12 keer in Part 2
- 24 h urine collection: 8x in Part 1, 9x in Part 2
- Complete questionnaires: 6x in Part 1, 8x in Part 2
Vaccination (if applicable): 1x

Optional:
- Pharmacogenicity (1x blood collection)

Side effects of research medication and inconveniences research procedures.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Female and male patients * 18 years of age with a biopsy-verified IgA nephropathy and where the biopsy was performed within the previous three years. If the most recent renal biopsy was performed
more than three years ago, a new biopsy should be performed.
* Patients must weigh at least 35 kg to participate in the study, and must have a body mass index (BMI) within the range of 15 - 38 kg/m2. BMI <=Body weight (kg) / [Height (m)]2
* Measured GFR or estimated GFR calculated using the CKD-EPI formula (or modified MDRD formula according to specific ethnic groups and local practice guidelines (Imai et al 2011)) *30 mL/min per 1.73 m2
* Urine protein to creatinine ratio (UPCR) *0.8 g/g (*90 mg/mmol) sampled from first morning void (FMV) or urine protein *0.75 g/24hr from a 24h urine collection at screening and urine protein *0.75 g / 24h from a 24h urine collection at the completion of the run- in period
* Vaccination against Neisseria meningitidis types A, C, Y and W-135 is required at least 4 weeks prior to first dosing with LNP023. Vaccination against N. meningitidis type B, S. pneumoniae and H. influenzae should be conducted if available and acceptable by local regulations, at least 4 weeks prior to first dosing with LNP023
* All patients must have been on supportive care including a maximally tolerated dose of ACEi or ARB therapy for the individual, antihypertensive therapy or diuretics for at least 90 days before dosing.

Exclusion criteria

* Presence of crescent formation in *50% of glomeruli assessed on renal biopsy
* Patients previously treated with immunosuppressive agents such as

cyclophosphamide, mycophenolate mofetil (MMF) or mycophenolate sodium, cyclosporine, tacrolimus, sirolimus or systemic corticosteroids within 90 days prior to start of LNP023/Placebo dosing
* All transplanted patients (any organ, including bone marrow)
* History of immunodeficiency diseases, or a positive Human Immunodeficiency Virus (HIV; ELISA and Western blot) test result.
* Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded
* Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject*s medical history and/or clinical or laboratory evidence of any of the following:
* A history of invasive infections caused by encapsulated organisms e.g. meningococcus or pneumococcus
* Splenectomy
* Inflammatory bowel disease, peptic ulcers, severe gastrointestinal disorder including rectal bleeding;
* Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
* Pancreatic injury or pancreatitis;
* Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase and serum bilirubin will be tested.
* Any single parameter of ALT, AST, GGT, alkaline phosphatase or serum bilirubin must not exceed 2 x upper limit of normal (ULN)
* Prothrombin Time / International normalized ration (PT/INR) must be within the reference range of normal individuals
Evidence of urinary obstruction or difficulty in voiding any urinary tract disorder other than IgAN that is associated with hematuria at screening; [If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error]
* Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
* A history of clinically significant electrocardiogram (ECG) abnormalities, or any of the following ECG abnormalities at screening or baseline:
* PR > 200 msec
* QRS complex > 120 msec
* QTcF > 450 msec (males)
* QTcF > 460 msec (females)
* History of familial long QT syndrome or known family history of Torsades de Pointes

* Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study
* History of severe allergic reactions as per Investigator decision
* Female patients who are pregnant or breastfeeding, or intending to conceive during the course of the study
* Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception from first dosing with LNP023 until an additional one week following cessation of study drug.
* History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
* History of any porphyria metabolic disorder

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):	26-09-2018
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LNP023

Generic name:	LNP023

Ethics review

Approved WMO Date:	09-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2019
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	21-10-2020
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	EUCTR2017-000891-27-NL
ClinicalTrials.gov	NCT03373461
CCMO	NL65098.056.18