A randomized, multicenter, active-comparator controlled, open-label trial to evaluate efficacy and safety of oral, twice daily LNP023 in adult patients with PNH and residual anemia, despite treatment with an intravenous anti-C5 antibody

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haemolyses and related conditions
Study type	Interventional

Summary

ID

NL-OMON51938

Source
ToetsingOnline

Brief title
CLNP023C12302

Condition

- Haemolyses and related conditions

Synonym
hemolysis red blood cells, PNH

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: anti-C5 antibody, complement inhibitor, LNP023, PNH

Outcome measures

Primary outcome

Endpoint(s) for primary objective(s)

• Response defined as having an increase from baseline in Hb >= 2 g/dL assessed between Day 126 and Day 168, in the absence of packed red blood cell transfusions between Day 14 and Day 168

• Response defined as having Hb >= 12 g/dL between Day 126 and Day 168 in the absence of packed-red blood cell transfusions between Day 14 and Day 168

Secondary outcome

Endpoint(s) for secondary objective(s)

• Absence of administration of packed-red blood cell transfusions between Day 14 and Day 168

• Change from baseline in hemoglobin (g/dL) as mean of visits between Day 126 and Day 168

• Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168

• Change from baseline in reticulocyte count (109/L) as mean of visits between Day 126 and Day 168

• Percent change from baseline in LDH levels (U/L) as mean of visits between

Day 126 and Day 168

• Occurrences of breakthrough hemolysis reported between Day 1 and Day 168

• Occurrences of MAVEs occurring between Day 1 and Day 168

Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hemolytic disorder characterized by complement-mediated intravascular hemolysis, bone marrow failure (BMF) and severe thrombophilia.The clinical presentation is driven by uncontrolled complement activation on CD55 and CD59 deficient PNH type RBC. Thromboembolism is the leading cause of morbidity and mortality in patients with PNH and can occur at any site.
Eculizumab is approved anti-C5 antibody therapie for the treatment of PNH and the current Standard of Care (SoC).
There is a heterogeneous hematological response with eculizumab and a substantial proportion of patients does not achiev normal or near normal hemoglobin levels. The heterogeneous response to eculizumab or other anti-C5 antibody treatment can, in part, be explained through its mechanism of action inhibiting intravascular hemolyse. LNP023 has the potential to prevent both intra- and extravascular hemolysis, and therefore, offer therapeutic benefits over and above the current SoC.
In this study the SoC is compared to LNP023 treatment. The main goal is to determine whether LNP023 is efficacious and safe for the treatment of PNH. LNP023 has not yet been approved ("registered") by the Dutch government as a drug. Doctors are not allowed to prescribe LNP023. Patient studies are required for registration. To date, approximately 102 healthy subjects and 29 patients with PNH have been treated with LNP023 in studies

Study objective

The aim of this study is to determine whether LNP023 is effective and safe for the treatment of PNH. LNP023 is compared to the Standard of Care (SOC) anti-C5 antibody treatment.
The primary objectives are to:
• Demonstrate superiority of LNP023 compared to anti-C5 antibody treatment in the proportion of participants achieving a sustained increase in hemoglobin levels from baseline of >= 2 g/dL in the absence of red blood cell transfusions.
• Demonstrate superiority of LNP023, compared to anti-C5 antibody treatment, in

the proportion of participants achieving sustained hemoglobin levels >= 12 g/dL in the absence of red blood cell transfusions.
The main clinical question of interest is: What is the treatment effect of LNP023 200mg bid versus anti-C5 treatment in PNH patients with residual anaemia. The endpoints here are:
- an increase in the Hb level from baseline by more than 2 g/dL
- and final HB levels in excess of 12g/dL. These measuring points are both assessed between day 126 and 168.
- the need for RBC transfusion on day 14 and day 168.

Study design

This study is a multi-center, randomized, open-label, active comparator-controlled, parallel group study, which is comprised of a screening period, a 24-week, active controlled, parallel group treatment period and a 24-week LNP023 treatment extension period.

Intervention

LNP023 200mg bid

Study burden and risks

- A screening period of up to 8 weeks (unless it is necessary to extend it for vaccinations However, it should be ticked off as soon as possible to avoid extending the screening period).
-A treatment period of 24 weeks and an extension period of 24 weeks. Participants who have started anti-C5 therapy may switch to LNP023 during the extension period. Patients who started with LNP023 may continue with LNP023 during the extension period.
The prolongation period is also 24 weeks and starts on the day after the end of the week 24 visit.

Participants who do not agree with the extension period have their last study visit around 24 weeks.

Based on 20 visits, the burden will be as follows:
Physical examinations, ECGs, Vital functions, blood tests, pregnancy tests, questionnaires. Vaccination if applicable: before the study and depending on previous vaccinations
Optional: pharmacogenetics 1

Side effects of research medication and inconvenient research procedures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Male and female participants >= 18 years of age with a diagnosis of PNH confirmed by high-sensitivity flow cytometry with RBCs and WBCs granulocyte/monocyte clone size >= 10%
- Stable regimen of anti-C5 antibody treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization
- Mean hemoglobin level <10 g/dL
- Vaccination against Neisseria meningitidis infection is required prior to the start of treatment.
- If not received previously, vaccination against Streptococcus pneumoniae and Haemophilus influenzae infections should be given

Exclusion criteria

- Participants on a stable eculizumab dose but with a dosing interval of 11 days or less
- Known or suspected hereditary complement deficiency at screening
- History of hematopoietic stem cell transplantation
- Patients with laboratory evidence of bone marrow failure (reticulocytes <100x109/L; platelets <30x109/L; neutrophils <500x106/L).
- Active systemic bacterial, viral (incl. COVID-19) or fungal infection within 14 days prior to study drug administration
- A history of recurrent invasive infections caused by encapsulated organisms, e.g. meningococcus or pneumococcus.
- Major concurrent comorbidities including but not limited to severe kidney disease (e.g. eGFR < 30 mL/min/1.73 m2, dialysis), advanced cardiac disease (e.g., NYHA class IV), severe pulmonary disease (e.g., severe pulmonary) hypertension (WHO class IV)), or hepatic disease (e.g., active hepatitis) that in the opinion of the investigator precludes participant's participation in the study.

Other protocol-defined inclusion/exclusion criteria may apply

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-01-2021
Enrollment:	2

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	LNP023
Generic name:	iptacopan
Product type:	Medicine
Brand name:	Soliris
Generic name:	Eculizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ultomiris
Generic name:	Ravulizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-11-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2021
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-06-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	16-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2019-004665-40-NL
ClinicalTrials.gov	NCT04558918
CCMO	NL74786.100.20