A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING EFFICACY AND SAFETY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) NOT PREVIOUSLY TREATED WITH COMPLEMENT INHIBITORS

Published: 19-08-2020
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This study has been transitioned to CTIS with ID 2023-506498-36-00 check the CTIS register for the current data. To evaluate the efficacy of crovalimab compared to eculizumab

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Red blood cell disorders
Study type	Interventional

Summary

ID

NL-OMON52285

Source
ToetsingOnline

Brief title
BO42162 (COMMODORE 2)

Condition

- Red blood cell disorders

Synonym
Paroxysmal nocturnal hemoglobinuria, PNH

Research involving
Human

Sponsors and support

Primary sponsor: F. Hoffmann- La Roche Ltd.
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: C5 inhibitor, Crovalimab, Eculizumab, Paroxysmal Nocturnal Hemoglobinuria

Outcome measures

Primary outcome

1. Proportion of patients who achieve transfusion avoidance

2. Proportion of patients with hemolysis control, measured by LDH <=1.5×ULN

Secondary outcome

1. Proportion of patients with breakthrough hemolysis

2. Proportion of patients with stabilization of hemoglobin

3. Mean change in fatigue as assessed through use of the Functional Assessment

of Chronic Illness Therapy (FACIT)-Fatigue scale

4. Incidence and severity of adverse events

5. Change from baseline in targeted vital signs

6. Change from baseline in targeted clinical laboratory test results

7. Incidence and severity of injection-site reactions, infusion-related

reactions, hypersensitivity, and infections

8. Incidence of adverse events leading to study drug discontinuation

9. Incidence and severity of clinical manifestations of drug-target-drug

complex formation in patients who switched to crovalimab treatment from

eculizumab or ravulizumab treatment

10. Serum concentration of crovalimab or eculizumab

11. Prevalence and incidence of anti-drug antibodies (ADAs) to crovalimab

12. Change over time in pharmacodynamic biomarkers

13. Change over time in free C5 concentration in crovalimab-treated patients

14. Observed value and absolute change in parameters reflecting hemolysis

Study description

Background summary

Paroxysmal nocturnal hemoglobinuria (PNH) is an ultra-rare, acquired, clonal, hematopoietic stem cell disorder. Due to a somatic mutation, hematopoietic cells (and progeny of affect stem cells) are deficient in proteins involved in complement regulation. This deficiency leads to inadequate blocking of the membrane attack complex (MAC), subsequently resulting in intravascular hemolysis.
Current treatment (with ravulizumab or eculizumab) for PNH is based on inhibition of C5, however about 35-50% of the patients treated with eculizumab still require regular transfusions. Therefore, there is still an unmet medical need.

Based on clinical data, nonclinical pharmacology, and pharmacodynamic (PD) data, crovalimab is expected to lead to consistent and complete complement protein C5 inhibition resulting in suppression of intravascular hemolysis at the targeted dosing regimens. Compared to ravulizumab and eculizumab, crovalimab binds to a different part of C5.

Study objective

This study has been transitioned to CTIS with ID 2023-506498-36-00 check the CTIS register for the current data.

To evaluate the efficacy of crovalimab compared to eculizumab

Study design

A Phase III, randomized, open-label, active-controlled, multicenter study of crovalimab in adult and adolescent patients with paroxysmal nocturnal hemoglobinuria (PNH).

Intervention

Subjects will be randomized 2:1 to crovalimab versus eculizumab.
For participants in the crovalimab group weighing 40-100 kg: Crovalimab will be administered intravenously on Day 1 (at 1000 mg) and during week 1-4 will be injected subcutaneously (at 340 mg) weekly. In week 5 and later, participants will receive 680 mg crovalimab subcutaneously every 4 weeks.
For participants in the crovalimab group weighing 100 kg or more: Crovalimab will be administered intravenously on Day 1 (at 1500 mg) and at Day 2 will be injected subcutaneously (at 340 mg). In weeks 2, 3 and 4, participants will receive 340 mg crovalimab weekly. Starting Week 5 and later, participants will receive 1020 mg crovalimab subcutaneously every 4 weeks.

For participants in the eculizumab group: participants will receive eculizumab as intravenous infusion weekly (600 mg) during weeks 1-4. Starting week 5 and up until week 25, participations will receive eculizumab through an IV every 2 weeks (at 900 mg).

Study burden and risks

The minimum duration of subject*s participation in this study:
- 52 weeks for those randomized to receive crovalimab
- 38 weeks for those randomized to receive eculizumab.
During the treatment period the subject in the crovalimab group, will have to visit the hospital weekly for the first 4 weeks. From week 5-25, the subject will have a visit every 2 weeks. After week 25, the subject will have a hospital visit every 8 weeks, and subsequently every 12 weeks for as long as they remain on the study.
For subjects randomized to the eculizumab group, weekly visits are scheduled for the first 4 weeks. Then every 2 weeks during weeks 5-25. Subsequently they can switch to receive crovalimab and will have visits as described for the crovalimab group.

Risks associated with crovalimab treatment include, but are not limited to, meningococcal infection, type III hypersensitivity reactions and infusion related reactions.
These side effects can be symptomatically treated.

For PNH patients, lifelong therapy is needed. Considering this, treatment with crovalimab can (potentially) reduce the treatment burden with optimal disease control, compared to treatment with eculizumab and ravulizumab. Current clinical experience indicates that the drug is well tolerated in naïve PNH

patients. Therefore, there is a positive overall risk-benefit for treatment with crovalimab.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

- Body weight >= 40 kg
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs
- LDH level >=2 x ULN at screening (as per local assessment)
- Vaccination against Neisseria meningitidis serotypes A, C, W, and Y < 3 years prior to initiation of study treatment. Vaccination against serotype B should be administered in accordance with the most current local

guidelines or SOC, as applicable in patients with complement deficiency. If not previously administered or no longer current, vaccination must be completed no later than one week after the first study drug administration. Vaccination currency with vaccination against serotypes A, C, W, Y and B should be maintained throughout the study, according to local guidelines or standard-of-care as applicable in patients with complement deficiency. In the absence of clear local guidelines for Neisseria meningitidis, the Advisory Committee on Immunization Practices 2020 Guidelines are recommended.
- Platelet count >= 30,000/mm*3 at screening without transfusion support within 7 days of lab testing.
- ANC > 500/micro L at screening
- For female patients of childbearing potential: agreement to remain abstinent or use contraception
Additional Inclusion Criteria for Patients in the Randomized Arms
-Age >=18 years
Additional Inclusion Criteria for Patients in the Descriptive Arm
- Age < 18 years

Exclusion criteria

- Current or previous treatment with a complement inhibitor
- History of allogeneic bone marrow transplantation
- History of Neisseria meningitidis infection within 6 months prior to screening and up to first study drug administration
- History of myelodysplastic syndrome with Revised International Prognostic Scoring System (IPSS-R) prognostic risk categories of intermediate, high and very high
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 46 weeks (approximately 10.5 months) after the final dose of crovalimab, or 3 months after final dose of eculizumab (or longer if required by the local product label)
- Concurrent disease, treatment, procedure, or surgery or abnormality in clinical laboratory tests that could interfere with the conduct of the study, may pose any additional risk for the patient, or would, in the opinion of the Investigator, preclude the patient's safe participation in and completion of the study
- Splenectomy <= 6 months prior to screening
- Positive for hepatitis B surface antigen at screening
- Positive for hepatitis C virus antibody at screening (confirmed by detectable viral RNA)
- History of or ongoing cryoglobulinemia at screening

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:	Recruiting
Start date (anticipated):	29-11-2021
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	Crovalimab
Product type:	Medicine
Brand name:	Soliris
Generic name:	Eculizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-08-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	07-01-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	26-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-12-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-08-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-01-2024
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
EU-CTR	CTIS2023-506498-36-00
EudraCT	EUCTR2019-004931-21-NL
CCMO	NL74837.056.20