A PHASE III, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER STUDY EVALUATING SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF CROVALIMAB VERSUS ECULIZUMAB IN PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) CURRENTLY TREATED WITH COMPLEMENT INHIBITORS

Published: 19-08-2020
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This study has been transitioned to CTIS with ID 2023-506526-37-00 check the CTIS register for the current data. To evaluate the safety and tolerability of crovalimab compared witheculizumab

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

Summary

ID

NL-OMON54448

Source
ToetsingOnline

Brief title
BO42161 (COMMODORE 1)

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. Incidence and severity of adverse events

2. Change from baseline in targeted vital signs

3. Change from baseline in targeted clinical laboratory test results

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

reactions, hypersensitivity, and infections

5. Incidence of adverse events leading to study drug discontinuation

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

complex formation in patients who switched to crovalimab treatment

from eculizumab or ravulizumab treatment

Secondary outcome

1. Serum concentration of crovalimab or eculizumab

2. Serum concentration of ravulizumab

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

crovalimab

4. Change over time in pharmacodynamic biomarkers

5. Change over time in free C5 concentration in crovalimab-treated

patients

6. Observed value and absolute change in parameters reflecting

hemolysis

7. Percent change from baseline in LDH level averaged over Weeks 21,

23, and 25 LDH measurements

8. Proportion of patients with transfusion avoidance

9. Proportion of patients with breakthrough hemolysis

10. Proportion of patients with stabilization of hemoglobin

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

Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale

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 2023-506526-37-00 check the CTIS register for the current data.

To evaluate the safety and tolerability of crovalimab compared with 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 1:1 to crovalimab (Arm A) versus eculizumab (Arm B) or will be assigned to Arm C if younger than 18 or if they meet specific criteria.
For participants in Arm A and C 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 Arm A and C 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 Arm B: participants will receive eculizumab at the same dose and schedule as they were on before the study (IV infusion, every 2 weeks).

Study burden and risks

The minimum duration of subject*s participation in this study:
- 52 weeks for those randomized/enrolled to receive crovalimab
- 38 weeks for those randomized to receive eculizumab.
During the treatment period the subject in Arms A and C, 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 Arm B, weekly visits are scheduled for the first 4 weeks. Then every 2 weeks during weeks 5-9, and after week 9, they will have a visit every 4 weeks until week 25. Subsequently they will have visits every 12 weeks.

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. 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)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Body weight >= 40 kg
- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation of WBCs,
- Vaccination against Neisseria meningitidis serotypes A, C, W, and Y < 3 years prior to initiation of study treatment, or, if not previously done, vaccination administered no later than one week after the first drug administration. Vaccination currency should be maintained throughout the study in accordance with most current local guidelines or standardofcare
as applicable in patients with complement deficiency
- Vaccination against Haemophilus influenzae type B and Streptococcus pneumoniae according to national vaccination recommendations
- 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
For Patients in Randomized Arms (Arm A and B)
- Age >= 18 years
- Documented treatment with eculizumab according to the approved dosing recommended for PNH and completion of a minimum of 24 weeks of treatment prior to Day 1
- Lactate dehydrogenase (LDH) <= 1.5 × ULN at screening
For Patients in Non Randomized Arm (Arm C)
- Age <18 old, currently treated with eculizumab OR
- Currently treated with ravulizumab OR
- Currently treated with eculizumab at higher-than-approved doses OR
- Patients with known C5 polymorphism and poorly controlled hemolysis by eculizumab or ravulizumab
-Adult patients currently treated with approved doses of eculizumab
LDH <= 1.5 × ULN at screening

Exclusion criteria

- Major Adverse Vascular Event within 6 months prior to first drug

administration (Day 1)
- History of allogeneic bone marrow transplantation,
- 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) prognosticrisk 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 the 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 HCV 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):	31-08-2021
Enrollment:	4

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:	24-04-2021
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:	14-04-2023
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	CTIS2023-506526-37-00
EudraCT	EUCTR2020-000597-26-NL
CCMO	NL74836.056.20