A RANDOMIZED DOUBLE-BLIND PHASE IIA STUDY EVALUATING THE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF CROVALIMAB AS ADJUNCT TREATMENT IN PREVENTION OF VASO-OCCLUSIVE EPISODES (VOE) IN SICKLE CELL DISEASE (SCD)

Published: 23-01-2023
Last updated: 14-09-2024

This study has been transitioned to CTIS with ID 2022-502542-28-00 check the CTIS register for the current data. This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab compared with placebo as adjunct...

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

Summary

ID

NL-OMON53710

Source
ToetsingOnline

Brief title
BO42451/ Crosswalk-C

Condition

- Red blood cell disorders
- Blood and lymphatic system disorders congenital

Synonym

sickle cell anaemia, Sickle Cell Disease (SCD)

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffman - La Roche

Intervention

Keyword: Crovalimab, pain attack (crisis), Prevention of vaso-occlusive episodes, Sickle Cell Disease

Outcome measures

Primary outcome

The primary efficacy objective for this study is to evaluate the efficacy of

crovalimab compared with placebo on the basis of the following endpoint:

Annualized rate of medical facility VOEs (AVR).

Secondary outcome

1. Annualized rate of home VOE captured by patient report

2. Annualized rate of uncomplicated medical facility VOE

3. Annualized rate of acute chest syndrome (ACS)

4. Annualized rate of days hospitalized for medical facility VOE

5. Annualized rate of days hospitalized for treatment of non-VOE complications

of SCD

6. Change in hematologic measures from baseline to Week 49

7. Time to first medical facility VOE from randomization

8. Change in urinary albumin-creatinine ratio from baseline to Week 49

9. Change from baseline to Week 49 in tricuspid regurgitant jet velocity (TRV)

10. Proportion of patients with TRV >2.5 m/s at Week 49

11. Change from baseline to Week 49 in Patient-Reported Outcomes Measurement

Information System (PROMIS)-Fatigue score in adults

Please refer to Protocol Section 2. Objectives and Endpoints for Exploratory

efficacy, Safety, Phamacokinetic, Immunogenicity and Biomarker objectives.

Study description

Background summary

The available data from patients with SCD, and in vitro and in vivo nonclinical models indicate that complement is activated in patients with SCD and suggest a role in its pathophysiology in multiple domains. Complement activation is detected in patients at steady state in SCD and has also been described in association with acute VOE. In vitro and in vivo models of complement inhibition suggest multiple potential downstream effects of C5 inhibition in patients with SCD that include prevention of endothelial activation by free heme, reduction in rate of hemolysis, reduction in vaso-occlusion, improvement in chronic inflammation, and reduction in end-organ damage.

Published evidence supports exploratory trials of complement inhibition in patients with SCD, which may address the unmet medical need in this disease, employing a mechanism that does not overlap with current therapies. Crovalimab induces rapid and complete inhibition of the terminal complement pathway by targeting C5, making it a suitable candidate for exploration of the role of targeting complement in treatment for
SCD.

Please also refer to chapter 1.1, 1.2 and 1.3.1 of the protocol.

Study objective

This study has been transitioned to CTIS with ID 2022-502542-28-00 check the CTIS register for the current data.

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab compared with placebo as adjunct treatment for the prevention of vaso-occlusive episodes (VOEs) in patients with sickle cell disease (SCD).

Study design

The study will enroll approximately 90 patients at approximately 30 sites globally. The screening period of the study will be up to 28 days in length. Patients who do not meet the criteria for participation in this study (screen failure) may qualify for two rescreening opportunities (for a total of three screenings per patient) at the investigator*s discretion.

This study has three parts:
1. Screening to assess the eligibility for the study (up to 28 days)
2. Treatment (48 weeks)
3. Follow-up to check on patients after treatment is finished

Eligible patients will be randomized 1:1 to receive either crovalimab or placebo in addition to their current SCD therapy. Patients in both treatment arms will receive standard treatment for SCD as guided by the treating physician and/or institutional guidelines, including but not limited to treatments currently approved for SCD within each country participating in this study.

After completing 48 weeks of study treatment, or, if patients stopped study treatment at any time, they will return to the clinic for a safety follow-up visit 24 weeks after the final dose of the study treatment. Also, a safety follow-up telephone call will be conducted at 46 weeks after the last dose of study treatment.

Intervention

The investigational medicinal products (IMPs) for this study are crovalimab and placebo.

The first dose of the study drug will be given as an IV infusion (into the vein) and will last approximately 1 hour (at W1D1). All other doses after this will be given as an injection under the skin. For subcutaneous injection, the crovalimab solution is used undiluted. For IV infusion, the crovalimab solution (2 mL or 340 mg (nominal) crovalimab) is diluted in 0.9% (w/v). Patients in placebo group will receive the same volume as weight-based crovalimab by IV infusion and injection under the skin.

Patients in this study will receive crovalimab according to a weight-based tiered dosing approach schedule for 48 weeks:

The first dose of the study drug (crovalimab or placebo) according to a weight-based dosing approach:
-1000 mg IV(60 ± 10 minutes) for patients whose weight is >= 40 kg to < 100 kg and,

-1500 mg IV (90 ± 10 minutes) for patients whose weight is >= 100 kg

Afterwards, they will get one injection (2 mL) under the skin on W1D2, W2,W3 and W4. At Week 5 and every 4 weeks onwards the dose will be:
- Two injections of 2 mL each (4 mL total) under the skin for patients whose weight is >= 40kg to <100kg and,
- Three injections of 2 mL each (6 mL total) under the skin for patients >= 100kg.

Study burden and risks

Published evidence supports exploratory trials of complement inhibition in patients with SCD, which may address the unmet medical need in this disease, employing a mechanism that does not overlap with current therapies. Crovalimab induces rapid and complete inhibition of the terminal complement pathway by targeting C5, making it a suitable candidate for exploration of the role of targeting complement in treatment for SCD.

Nonclinical findings and published evidence for safety of C5 inhibition in asplenic patients (described above) support the use of crovalimab in patients with SCD, with a preliminary safety profile of crovalimab assessed in the Phase I/II clinical study in PNH. The safety risk is considered to be manageable with patient selection, prevention by immunization and use of prophylactic antibiotics where indicated, long-term safety monitoring, strict guidance for early evaluation and intervention, and ongoing patient education measures. In addition, early mandatory reporting of sentinel events and ongoing safety assessments will provide an ongoing assessment of the risk and allow for optimization of the risk minimization approach where, or, if needed.
Hence, the benefit-risk profile to participants in this study is considered acceptable.

Please refer to Section 1.3.1 and 1.3.2. protocol: Study rational and benefit-risk assessment of the protocol for further details.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Signed ICF
- Age >= 12 to <= 55 years
- Body weight >= 40 kg
- Male or female with confirmed diagnosis of HbSS (SCD genotype of sickle cell anemia) or HbSβ0 (SCD genotype of sickle cell beta zero thalassemia)
- Two or more (>= 2) to <=10 documented VOEs in the 12 months prior to randomization
- If receiving concurrent SCD-directed therapy, the patient must have been on a stable dose for a minimum of 3 months prior to study enrollment. There should be no plans to modify the patients' dosing throughout the study duration, other than for safety reasons.
- If receiving erythropoietin, the patient must have been prescribed this medication for the preceding 3 months and be dose-stabilized for at least 3 months prior to study enrollment
- Vaccination against N. meningitides serotypes A, C, W and Y
- Vaccinations against H. influenza type B and S. pneumonia
- Patients who have been vaccinated (partially or in full) against SARSCoV-2 with a locally approved vaccine are eligible to be enrolled in the study, 3 days or longer after inoculation
- Adequate hepatic and renal function
- For women of childbearing potential, agreement to remain abstinent or use contraception during the treatment period and for 46 weeks (approximately 10.5 months) after the final dose of study treatment

Exclusion criteria

- History of hematopoietic stem cell transplant
- Participating in a chronic transfusion program and/or planning on undergoing an exchange transfusion during the duration of the study
- History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in the study treatment
- Received active treatment on another investigational trial within 28 days (or within five half-lives of that agent, whichever is greater) prior to screening visit, or plans to participate in another investigational drug trial
- Hemoglobin <6 g/dL
- Known or suspected hereditary complement deficiency
- Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration
- Presence of fever (>= 38 degrees Celsius) within 7 days before the first drug administration
- Immunized with a live attenuated vaccine within 1 month before first drug administration
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 46 weeks (approximately 10.5 months) after the final dose of study treatment
- Known HIV infection with documented CD4 count <200 cells/microliter within 24 weeks prior to screening
- History of N. meningitidis infection within the prior 6 months

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:	Pending
Start date (anticipated):	14-04-2023
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Crovalimab
Generic name:	RO7112689

Ethics review

Approved WMO Date:	23-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-06-2023
Application type:	First submission
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	CTIS2022-502542-28-00
EudraCT	EUCTR2020-004839-25-NL
ClinicalTrials.gov	NCT05075824
CCMO	NL83160.056.23