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A study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab for the management of acute uncomplicated vaso-occlusive episodes in participants with sickle cell disease

Submission date
22/02/2022

Recruitment status
No longer recruiting

Registration date
07/07/2022

Overall study status
Completed

Last Edited
22/10/2024

Condition category
Haematological Disorders

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Sickle cell disease (SCD) is a genetic disorder leading to red blood cells that distort into a sickled shape, contributing to painful vaso-occlusive episodes (VOEs). The purpose of this clinical trial is to look at the safety and effectiveness of crovalimab, and to understand the way your body processes (pharmacokinetics) and reacts (pharmacodynamics) to crovalimab.

Who can participate?
People aged 12 to 55 years with a confirmed diagnosis of sickle cell anemia (HbSS or HbSβ0)

What does the study involve?
Everyone who joins this clinical trial will receive ONLY one dose of either:
Crovalimab as a single infusion into the vein, OR
Placebo as a single infusion into the vein
The patients will have a 2 in 3 (67%) chance of being in the crovalimab group and a 1 in 3 (33%) chance of being in the placebo group.
During the clinical trial, participants can continue to have standard treatment for the pain attack (crisis) as recommended by the clinical trial doctor.
This is a 'placebo-controlled' clinical trial, which means that one of the groups will be given a saline (salt water) infusion with no active ingredients (also known as 'placebo'). A placebo is used as a control, to make sure any health effects are from the clinical trial treatment rather than other factors.
Neither the participant nor the site staff can choose or know which group they are in. An exception is made if the clinical trial doctor needs to know which group the participant is in for safety reasons.
While the participant is in the hospital for treatment for the sickle cell pain attack (crisis), they will be seen by the clinical trial doctor.

After being given treatment with crovalimab or a placebo, the participant will have regular tests and check-ups while hospitalised until they are well enough to go home from the hospital (discharged).
Once the participant is discharged from the hospital, they will have 5 telephone check-ups and 2 clinic visits with the clinical trial doctor to check on their health and any side effects they may be having.
The clinical trial will last for a total of 322 days (approximately 10.5 months) after the participant is given clinical trial treatment (crovalimab or placebo).

What are the possible benefits and risks of participating?
As with any study, there are risks (both known and unknown) associated with the drug or procedures used. Before starting the clinical trial, participants will be told about any risks and benefits of taking part in the trial. The participants will also be told what other treatments are available so that they may decide if they still want to take part. Participants health may or may not improve in this study, but the information that is learned may help other people who have a similar medical condition in the future. The potential side effects related to the study drug, based on laboratory studies, knowledge of similar drugs, or studies in other diseases, are listed below:
1. Increased risk of infection, including Neisseria meningitidis infection
2. Allergic reactions
3. Infusion-related reactions
You may also receive antibiotics while taking part in this study. There may be risks to taking antibiotics:
1. Allergic reactions
2. Clostridium difficile infection
3. Development of resistant (unresponsive to treatment) bacteria in the body
It is possible that side effects of crovalimab which are unknown at this time may occur during the study. Any new information that may affect participants' health or which may make the participants want to stop taking part in the study will be shared with them as soon as it becomes available. There may be a risk in exposing an unborn child to crovalimab, and all risks are not known at this time. Participants cannot take part in the study if they are pregnant or become pregnant.
Participants will be fully informed of the potential risks and burdens involved in taking part in this research study in the Participant Information Sheet and will be given opportunities to ask questions prior to consent and during their participation. Participants will be monitored throughout the study in order to minimize risks.

Where is the study run from?
F. Hoffmann-La Roche (Switzerland)

When is the study starting and how long is it expected to run for?
January 2021 to October 2025

Who is funding the study?
F. Hoffmann-La Roche (Switzerland)

Who is the main contact?
Reference Study ID Number: BO42452; https://forpatients.roche.com/, global-roche-genentechtrials@gene.com

Contact information

Type(s)
Public, Scientific, Principal investigator

Contact name
Dr . Clinical Trials

Contact details
Building 1, Grenzacherstrasse 124
Basel
Switzerland
CH-4058
+1 888-662-6728
global-roche-genentech-trials@gene.com

Additional identifiers

Clinical Trials Information System (CTIS)
2020-004840-27 / 2022-502546-26-00

Integrated Research Application System (IRAS)
1005134

ClinicalTrials.gov (NCT)
NCT04912869

Protocol serial number
BO42452, CPMS 46764

Study information

Scientific Title
A phase Ib randomized, placebo-controlled study evaluating the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab for the management of acute uncomplicated vaso-occlusive episodes (VOE) in patients with sickle cell disease (SCD)

Study objectives
Current study hypothesis as of 09/02/2023:

The study is designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and efficacy of crovalimab compared with placebo for the management of acute uncomplicated vasoocclusive episodes (VOE) in participants with sickle cell disease (SCD).

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Previous study hypothesis:

Objectives:
• To evaluate the safety of crovalimab compared with placebo
• To evaluate the pharmacokinetics (PK) of crovalimab
• To evaluate the pharmacodynamics (PD) of crovalimab

• To evaluate the efficacy of crovalimab compared with placebo
• To evaluate the immune response to crovalimab

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 23/05/2022, East of England - Cambridge and Hertfordshire Research Ethics Committee (Equinox House, City link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8265; cambsandherts.rec@hra.nhs.uk), ref: 22/YH/0061

Study design
Interventional double-blind randomized parallel group placebo controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Sickle cell disease (SCD); vaso-occlusive episodes in SCD; Pain crisis

Interventions
Current interventions as of 09/02/2023:

1. Crovalimab: Participants will receive a single intravenous (IV) infusion of Crovalimab based on body weight.
2. Placebo: Participants will receive a single IV infusion of a matching Placebo.

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Previous interventions:

Patients who meet all eligibility criteria and have consented for participation in the study will be randomized 2:1 to receive either a single intravenous (IV) tiered weight-based dose of crovalimab or placebo. Patients will be randomised via an online platform hosted by Clinphone.

A 2-step process for screening procedures is encouraged to preliminarily identify and consent patients for the study prior to VOE presentation, Screen Visit #1 (initial screen) is conducted at an outpatient visit (i.e., when the patient is not experiencing a VOE), where the main Informed Consent Form (ICF) is signed and preliminary eligibility is assessed. During this visit, preliminary screening assessments can be conducted, and a steady state SCD exploratory biomarker sample will be collected (only after consent is received). No additional assessments are required until Screen Visit #2. Eligibility at Screen Visit #1 does not guarantee eligibility at Screen Visit #2. Screen Visit #2 (VOE presentation screen) is then conducted when the patient presents with a VOE to the A/E department. The patient consent from Screen Visit #1 must be confirmed prior to starting study assessments (this confirmation must be documented). Once patient consent is confirmed, all remaining eligibility criteria must be assessed, and all screening assessments will be conducted .

Alternatively, if a patient is only first identified for participation in the study at presentation with a VOE, then all consent procedures (main ICF signature) and all screening assessments listed for both Screen Visit #1 and Screen Visit #2 (excluding the steady state SCD exploratory biomarker listed under Screen Visit #1) can be conducted at the same time after the patient presents in A/E.

If the patient meets all eligibility criteria then they are randomised and will receive treatment within 12 hours of presenting to A/E. Patients will be admitted to Hospital, Patients will be followed for the duration of the hospitalization until the time of discharge. After discharge, they will continue to be followed during an observational period on Days 14, 28, 46, 64, and 84 after study treatment administration; Days 14, 46, and 64 are telephone follow-ups and Days 28 and 84 are study site visits. The total duration of the study is 12 weeks (84 days) following administration of study treatment.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
crovalimab

Primary outcome(s)
Current primary outcome measure as of 09/02/2023:

1. Percentage of participants with adverse events (AEs), measured from Baseline up to Day 322
2. Percentage of participants with infusion-related reactions and hypersensitivity, measured from Baseline up to Day 84

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Previous primary outcome measure:

Incidence and severity of adverse events, with severity determined according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) measured at Screening visit 2, during study treatment, within 30 mins post-infusion, 12 hours post-infusion, day 2 - day 14, day of discharge, post-discharge day 28, day 46, day 64, and day 84

Key secondary outcome(s))
Current secondary outcome measures as of 09/02/2023:

1. Time to improvement of the primary acute uncomplicated VOE, measured from Baseline up to Day 84
2. Total cumulative opioid dose, measured from Baseline up to Day 84
3. Time to discontinuation of all parenteral opioids, measured from Baseline up to Day 84
4. Time to readiness for hospital discharge, measured from Baseline up to Day 84
5. Time to hospital discharge, measured from Baseline up to Day 84
6. Time to a confirmed decrease in pain score of at least 2 points from the maximal pre-dose pain score, measured from Baseline up to Day 84
7. Change in pain score from the maximal pre-dose pain score to the score at hospital discharge,

measured from Baseline up to Day 84
8. Percentage of participants who develop acute chest syndrome (ACS), measured from Baseline up to Day 28
9. Percentage of participants requiring intensive care unit (ICU)/critical care admission for SCD-related complications, measured from Baseline up to Day 84
10. Percentage of participants requiring blood transfusion for SCD-related complications, measured from Baseline up to Day 84
11. Readmission rate for a VOE or VOE-related event within 28 days of discharge of the primary VOE, measured from Baseline up to Day 84
12. Serum concentrations of crovalimab over time, measured from Baseline up to Day 84
13. Change in PD Biomarkers including complement activity (CH50)s over time, measured from Baseline up to Day 84
14. Change over time in free C5 concentration, measured from Baseline up to Day 84
15. Change over time in soluble complement 5b 9 (sC5b-9) concentration, measured from Baseline up to Day 84
16. Percentage of participants with anti-drug antibodies to crovalimab, measured from Baseline up to Day 84

Previous secondary outcome measures:

Change from baseline in targeted vital signs and clinical laboratory test results :
1. Vital signs (temperature, pulse, and blood pressure) at Screening visit 2, during study treatment, within 30 mins post-infusion, 12 hours post-infusion, day 2 - day 14, day 28, and Day 84
2. Clinical lab tests (Hematology (including reticulocytes), Chemistry (including LDH), Serum PK sample, Serum ADA sample, Plasma and serum PD samples, and Blood sample for clinical genotyping) at screening visit 2, day 2, day6, day 10, day 14, day if discharge, day 28, and day 84
3. Incidence and severity of infusion-related reactions and hypersensitivity, will be measured during the infusion and also post-infusion, depending on the incidence and the severity of the infusion

Completion date
31/10/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 15/10/2024:

1. Age >=12 to =<55 years
2. Body weight >=40 kg
3. Confirmed diagnosis of HbSS (SCD genotype of sickle cell anemia) or HbSβ0 (SCD genotype of sickle cell beta zero thalassemia)
4. Vaccination against Neisseria meningitidis
5. Vaccinations against H. influenzae type B and S. pneumoniae
6. Participants vaccinated against SARS-CoV-2 are eligible, as long as it has been 3 days or more after inoculation with the vaccine.
7. Diagnosis of an acute uncomplicated VOE, that requires admission to a hospital/acute medical facility and treatment with parenteral opioid analgesics

8. Adequate hepatic and renal function
9. Hemoglobin >=5 grams/deciliter (g/dL)
10. Platelet count >=100,000/microliter (µL)
11. Participants receiving SCD-directed therapies must be on a stable dose for >=28 days
12. For female participants of childbearing potential, an agreement to remain abstinent or use contraception for 6 months after the dose of study treatment

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Previous inclusion criteria as of 09/02/2023:

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7. Diagnosis of an acute uncomplicated VOE, that requires admission to a hospital/acute medical facility and treatment with parenteral opioid analgesics
8. Adequate hepatic and renal function
9. Hemoglobin >=5 grams/deciliter (g/dL)
10. Platelet count >=100,000/microliter (µL)
11. Participants receiving sickle cell therapies must be on a stable dose for >=28 days
12. For female patients of childbearing potential, an agreement to remain abstinent or use contraception for 6 months after the dose of study treatment

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Previous inclusion criteria:

1. Signed ICF or Assent Form (as determined by patient's age and individual site and country standards)
2. Age >=12 to =<55 years
3. Body weight >=40 kg
4. Confirmed diagnosis of HbSS (SCD genotype of sickle cell anemia) or HbSβ0 (SCD genotype of sickle cell beta zero thalassemia)
5. Vaccination against Neisseria meningitidis
6. Vaccinations against H. influenzae type B and S. pneumoniae
7. Diagnosis of an acute uncomplicated VOE, that requires admission to a hospital/acute medical facility and treatment with parenteral opioid analgesics
8. Adequate hepatic and renal function
9. Hemoglobin >=5 g/dL
10. Platelet count >=100,000/µL
11. Patients receiving sickle cell therapies must be on a stable dose for >=28 days
12. For female patients of childbearing potential, an agreement to remain abstinent or use contraception for 6 months after the dose of study treatment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 years

Upper age limit
55 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 15/10/2024:

1. More than 10 VOEs within the last 12 months prior to presentation, that have required a medical facility visit
2. Pain related to the current VOE ongoing for >36 hours
3. Acute pain related to avascular necrosis, hepatic or splenic sequestration, or priapism
4. Pain atypical of an acute uncomplicated VOE
5. Evidence of or suspicion of ACS
6. Evidence or high suspicion of a severe systemic infection
7. Major surgery and/or hospitalization for any reason within 30 days
8. History of Neisseria meningitidis infection within 6 months prior
9. Known HIV infection with a documented CD4 count <200 cells/μL
10. Transfusion or receipt of blood products within 3 months or current participation in a chronic transfusion protocol
11. Immunized with a live attenuated vaccine within 30 days
12. History of hematopoietic stem cell transplant
13. Known or suspected hereditary complement deficiency
14. Pregnant or breastfeeding, or intending to become pregnant during the study or within 322 days (approximately 10.5 months) after the study drug administration.
15. Participation in another interventional treatment study with an investigational agent or use of any experimental therapy within the prior 28 days or within five half-lives of that investigational product, whichever was greater

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Previous exclusion criteria as of 09/02/2023:

1. More than 10 VOEs within the last 12 months prior to presentation, that have required a medical facility visit
2. Pain related to the current VOE ongoing for >48 hours
3. Acute pain related to avascular necrosis, hepatic or splenic sequestration, or priapism
4. Pain atypical of an acute uncomplicated VOE
5. Evidence of or suspicion of ACS
6. Evidence or high suspicion of a severe systemic infection
7. Major surgery and/or hospitalization for any reason within 30 days

8. History of Neisseria meningitidis infection within 6 months prior
9. Known HIV infection with a documented CD4 count <200 cells/µL
10. Transfusion or receipt of blood products within 3 months or current participation in a chronic transfusion protocol
11. Immunized with a live attenuated vaccine within 30 days
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Date of first enrolment
26/03/2022

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

Brazil

France

Italy

Kenya

Lebanon

Netherlands

South Africa

Spain

United States of America

Study participating centre
Azienda Ospedaliera di Verona-Policlinico G.B. Rossi; Medicina Interna
Verona Veneto
Italy
371734

Study participating centre
Hospital General Univ. Gregorio Maranon
Madrid
Spain
28009

Study participating centre
Hospital Universitario Virgen del Rocio; Servicio de Hematologia
Sevilla
Spain
41013

Study participating centre
CHU Henri Mondor; Service de médecine interne
Créteil
France
94010

Study participating centre

Hôpital Saint Eloi; Service de Médecine interne
Montpellier
France
34295

Study participating centre
Icahn School of Medicine at Mount Sinai
New York City
United States of America
10029

Study participating centre
East Carolina University; Brody School of Medicine
Greenville
United States of America
27834

Study participating centre
Hospital Sao Rafael – HSR
Salvador
Brazil
41253-190

Study participating centre
Hospital das Clinicas – UFRGS
Porto Alegre
Brazil
90035-903

Study participating centre
Hospital de Base de Sao Jose do Rio Preto
Sao Jose do Rio Preto
Brazil
15090-000

Study participating centre
The Whittington Hospital
Highgate Hill
London

United Kingdom
N19 5NF

Study participating centre
University College Hospital
235 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
Hospital Universitario Miguel Servet; Servicio Hematologia
Zaragoza
Spain
50009

Study participating centre
Children's Healthcare of Atlanta
Atlanta
United States of America
30322

Study participating centre
Amsterdam UMC Location VUMC
Amsterdam
Netherlands
1105 AZ

Study participating centre
International Cancer Institute (ICI)
Eldoret
Kenya
30100

Study participating centre
Gertrude’s Children’s Hospital
Nairobi
Kenya
00100

Study participating centre
American University of Beirut - Medical Center
Hazmeih
Lebanon
1003

Study participating centre
Hopital Nini
Tripoli
Lebanon
-

Study participating centre
Charlotte Maxeke Johannesburg Hospital; Haemophilia Comprehensive Care Center
Johannesburg
South Africa
2193

Sponsor information

Organisation
F.Hoffmann-La Roche Ltd.

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes