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A study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab as an adjunct treatment in the prevention of vaso-occlusive episodes in sickle cell disease

Submission date
20/05/2022

Recruitment status
No longer recruiting

Registration date
02/08/2022

Overall study status
Completed

Last Edited
04/12/2023

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 (SDC) is a disorder of the structure of haemoglobin found in red blood cells and is a serious lifelong condition. Although treatment and survival of SCD have improved, there is still a need to improve treatments for people living with SCD, particularly in the chronic setting. Crovalimab is a new experimental drug which may help to decrease inflammation and destruction of red blood cells and may improve episodes of pain attack (crisis). The aim of this study is to compare the effects, good and bad, of crovalimab versus placebo (dummy drug).

Who can participate?
Patients aged between 12- 55 years old with SCD experiencing a pain attack

What does the study involve?
Participants will receive either crovalimab or placebo. A placebo looks like a drug but has no active ingredient. The treatment group is decided by chance using a computer program. Neither the participant nor the study staff can choose or know which treatment group is allocated.
The study has three stages:
1. Screening: to see if the patient is eligible for the study
2. Treatment: with crovalimab or placebo, initially given as an infusion into the vein, then as an injection in the skin over a period of 48 weeks
3. Follow-up period of 24 weeks to check on the participant's response and their health
The total time in the study will be about 1 year and 6 months, which includes the screening, treatment and follow-up visits.

What are the possible benefits and risks of participating?
There are risks, discomforts, and inconveniences associated with any research study. It is possible that these general risks could be increased by the addition of test medications. Some of

the general risks may be potentially life-threatening and may not have been previously reported. Some of these procedures take place more often than they would if patients were not taking part in this study. Taking blood samples may cause bruising and discomfort and a risk of infection or blood clots at the site of the blood collection. If patients have a central line, this may be used for blood samples. There is always a risk of infection at the site where the line is fitted. Crovalimab will be given in a clinic with emergency equipment and staff who are trained to monitor for and respond to any potential medical emergencies. Side effects can be referred to in the main PIS ICF due to the character count limit. Treatment with crovalimab may increase the risk of infection by the bacteria Neisseria meningitidis (also known as a meningococcal infection). Meningococcal infections can be life-threatening, especially if not treated early. To reduce the risk of meningococcal infections, all patients in the study need to be vaccinated against Neisseria meningitidis. There may be a risk of infusion-related reactions with intravenous crovalimab administration This may occur during, shortly after, or within 24 hours of receiving crovalimab. To reduce any risk participants will be observed for 1 hour after the infusion is complete. During the study, crovalimab will also be given by an injection under the skin (called subcutaneous administration). There is a possible risk of injection-site reactions. To help reduce any risk participants will be observed for at least 1 hour after the first three injections under the skin. Participants may be required to receive antibiotics to prevent infections, depending on which antibiotic they receive, they may experience side effects associated with antibiotic therapy. There could be an allergic reaction, which can range from a mild rash to severe life-threatening anaphylaxis. There could be a risk of developing Clostridium difficile infection, which is a gastrointestinal infection characterised by abdominal pain, diarrhoea, and fever, which in some cases is difficult to treat and, in rare cases, could be fatal. The use of antibiotics could cause the development of resistant (unresponsive to treatment) bacteria in the body. This could lead to an infection, which may be difficult to treat and, in rare cases, could be fatal. 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. Patients cannot take part in the study if they are pregnant or become pregnant. Patients will be informed of all of the above risks in the Patient Information Sheet and will be asked to notify their study doctor or study staff should they experience any side effects during the study. Patients will be monitored throughout the study in order to minimise 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?
February 2021 to May 2025

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

Who is the main contact?
Dr Ramneet Jagdev, welwyn.uk_ethics@roche.com

Contact information

Type(s)
Scientific

Contact name
Dr Reference Study ID Number: BO42451 https://forpatients.roche.com/

Contact details
None available
None available
United States of America
None available
+1 888-662-6728 (U.S. and Canada)
global-roche-genentech-trials@gene.com

Additional identifiers

Clinical Trials Information System (CTIS)
2020-004839-25

Integrated Research Application System (IRAS)
1005491

Central Portfolio Management System (CPMS)
52468

Protocol serial number
BO42451

Study information

Scientific Title
A randomized double-blind Phase IIa study evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of crovalimab as an adjunct treatment in the prevention of vaso-occlusive episodes in sickle cell disease

Acronym
BO42451

Study objectives
1. To evaluate the efficacy of crovalimab compared with placebo
2. To evaluate the efficacy of crovalimab compared with placebo
3. To evaluate the safety and tolerability of crovalimab compared with placebo
4. To evaluate the pharmacokinetics of crovalimab
5. To evaluate the immune response to crovalimab

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/05/2022, East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (Equinox House, City link, Nottingham, NG2 4LA, UK; +44 (0)2071048096, +44 (0)207 104 8102, +44 (0)207 104 8265; cambsandherts.rec@hra.nhs.uk), ref: 22/EE/0139

Study design
Double-blind randomized 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

Interventions
Eligible patients will be randomized 1:1 to receive either crovalimab or placebo in addition to their current SCD therapy. Randomisation is via the IXRS system. 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 (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor), pain management treatment (e.g., opioid analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs]), hydration, oxygen, and other BSC.

Stratification factors at randomization are:
1. Number of vasoocclusive pain events (VOEs) in the 12 months prior to enrollment (4 vs 4 VOEs)
2. Use of concurrent SCD-directed therapy in any combination (e.g., hydroxyurea, L-glutamine, crizanlizumab, or voxelotor) (yes vs no)

An initial crovalimab (or matching placebo) intravenous (IV) loading dose will be administered on Week 1 Day 1 followed by 4 once-weekly subcutaneous (SC) doses of the study treatment (refers to crovalimab or placebo) on Week 1 Day 2, then on Weeks 2, 3, and 4. Maintenance dosing will begin at Week 5 and will continue Q4W thereafter, for a total of 48 weeks of treatment. All patients will receive the study treatment according to a weight-based tiered dosing schedule. Study treatment dosing will continue per protocol schedule during any medical facility or home VOE occurring on treatment.

For patients who discontinue the study treatment, a safety follow-up visit will be conducted at 24 weeks after the last dose of the study treatment.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Current primary outcome measures as of 07/03/2023:
Annualized rate of medical facility VOEs (AVR) measured using data recorded in the electronic case report forms (eCRFs) from Baseline to Week 49

Previous primary outcome measures:
Annualized rate of medical facility VOEs (AVR) up to 48 weeks. A medical facility VOE is defined as:
1. An uncomplicated medical facility VOE (defined as an acute episode of pain lasting at least 2 hours and occurring at least 3 days after return to the patient's chronic baseline pain levels, with no other medically determined cause other than a VOE that requires a medical facility visit and treatment with oral or parenteral opioids, parenteral nonsteroidal anti-inflammatory drugs [NSAIDs], or ketamine), OR
2. Acute chest syndrome (ACS), hepatic or splenic sequestration, or priapism requiring a visit to a medical facility.
Patients complete an e-diary and an HVQ sickle cell pain crisis questionnaire which will be reviewed and analysed by clinical scientists

Key secondary outcome(s))

Current secondary outcome measures as of 07/03/2023:
All outcomes will be measured from data recorded in the electronic case report forms (eCRFs) unless otherwise stated:
1. Annualized rate of home VOEs from Baseline to Week 49
2. Annualized rate of uncomplicated medical facility VOEs from Baseline up to Week 49
3. Annualized rate of acute chest syndrome (ACS) from Baseline up to Week 49
4. Annualized rate of days hospitalized for medical facility VOE from Baseline up to Week 49
5. Annualized rate of days hospitalized for treatment of Non-VOE complications of SCD from Baseline up to Week 49
6. Time to first medical facility VOE from randomization from Baseline up to Week 49
7. Change in urinary albumin-creatinine ratio from Baseline up to Week 49
8. Change in tricuspid regurgitant jet velocity (TRV) from Baseline to Week 49
9. Percentage of participants with TRV >2.5 m/s at Week 49
10. Change in Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue Score in adults from Baseline to Week 49
11. Percentage of participants with adverse events (AEs) up to 91 weeks
12. Serum concentrations of crovalimab over time from Baseline up to Week 49
13. Percentage of participants with anti-drug antibodies to crovalimab in serum from Baseline up to Week 49

Previous secondary outcome measures:
1. Annualized rate of home VOE captured on the patient's handheld device provided and questionnaires at baseline to Week 49
2. Annualized rate of uncomplicated medical facility VOE captured in the patients notes at baseline to Week 49
3. Annualized rate of acute chest syndrome (ACS) captured in the patients notes at baseline to Week 49
4. Annualized rate of days hospitalized for medical facility VOE captured in the patients notes at baseline to Week 49
5. Annualized rate of days hospitalized for treatment of non-VOE complications of SCD captured in the patients notes at baseline to Week 49
6. Hematologic measures measured using routine safety bloods from baseline to Week 49
7. Time to first medical facility VOE captured in the patients notes from randomization up to Week 49
8. Urinary albumin-creatinine ratio measured using review of routine safety bloods from baseline to Week 49
9. Tricuspid regurgitant jet velocity (TRV) measured using echocardiogram at baseline to Week

49
10. Proportion of patients with TRV >2.5 m/s measured using echocardiogram at Week 49
11. Fatigue measured using the Patient-Reported Outcomes Measurement Information System (PROMIS)-Fatigue score in adults at baseline to Week 49

Completion date
31/05/2025

Eligibility

Key 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. Male or female with confirmed diagnosis of HbSS (SCD genotype of sickle cell anemia) or HbSβ0 (SCD genotype of sickle cell beta zero thalassemia)
5. Two or more (≥2) to ≤10 documented VOEs in the 12 months prior to randomization
6. 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.
7. 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
8. Vaccination against N. meningitides, vaccinations against H. influenza type B and S. pneumonia
9. Patients who have been vaccinated (partially or in full) against SARS-CoV-2 with a locally approved vaccine are eligible to be enrolled in the study, 3 days or longer after inoculation
10. Adequate hepatic and renal function
11. For women of childbearing potential, agreement to remain abstinent or use contraception during the treatment period and for 6 months after the final 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

1. History of hematopoietic stem cell transplant
2. Participating in a chronic transfusion program and/or planning on undergoing an exchange transfusion during the duration of the study
3. History of hypersensitivity, allergic, or anaphylactic reactions to any ingredient contained in the study treatment
4. 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
5. Hemoglobin <6 g/dl
6. Known or suspected hereditary complement deficiency
7. Active systemic bacterial, viral, or fungal infection within 14 days before first drug administration
8. Presence of fever (≥38 degrees Celsius) within 7 days before the first drug administration
9. Immunized with a live attenuated vaccine within 1 month before first drug administration
10. Pregnant or breastfeeding, or intending to become pregnant during the study or within 6 months after the final dose of study treatment
11. Known HIV infection with documented CD4 count <200 cells/microliter within 24 weeks prior to screening
12 History of N. meningitidis infection within the prior 6 months

Date of first enrolment
08/12/2021

Date of final enrolment
31/07/2023

Locations

Countries of recruitment
United Kingdom

England

Brazil

France

Italy

Spain

Türkiye

Study participating centre
Northwick Park Hospital
Watford Road

Harrow
United Kingdom
HA1 3UJ

Study participating centre
UCLH
250 Euston Road
London
United Kingdom
NW1 2PQ

Study participating centre
Hammersmith Hospital
Du Cane Road
Hammersmith
London
United Kingdom
W12 0HS

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

Study participating centre
UNESP - Faculdade de Medicina da Universidade Estadual Paulista - Campus Botucatu
Botucatu, SP
Botucatu
Brazil
18618-970

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

Study participating centre
HEMORIO
Rio de Janeiro, RJ
Rio de Janeiro
Brazil
20211-030

Study participating centre
Hospital Samaritano
São Paulo
São Paulo
Brazil
01232-010

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

Study participating centre
Hospital das Clínicas Faculdades Médicas de Ribeirão Preto
Ribeirao Preto, SP
Ribeirao Preto
Brazil
14051-140

Study participating centre
Beneficencia Portuguesa de Sao Paulo
São Paulo, SP
São Paulo
Brazil
01321-00

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

Créteil
France
94010

Study participating centre
Hôpital Saint Eloi; Service de Médecine interne
Montpellier
Montpellier
France
34295

Study participating centre
Azienda Ospedaliera di Verona-Policlinico G.B. Rossi; Medicina Interna
Verona, Veneto
Verona
Italy
37134

Study participating centre
Ospedale Galliera; S.S.D. Ematologia
Genova, Liguria
Genova
Italy
16128

Study participating centre
Università degli Studi della Campania Luigi Vanvitelli; UOC Ematologia ed oncologia pediatrica
Napoli, Campania
Napoli
Italy
80138

Study participating centre
Hospital General Univ. Gregorio Maranon
Madrid
Madrid
Spain
28007

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

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

Study participating centre
Adana Acibadem Hospital; Pediatric Hematology
Adana
Adana
Türkiye
01130

Study participating centre
Cukurova University Medical Faculty Balcali Hospital
Adana
Adana
Türkiye
1330

Study participating centre
Mustafa Kemal University Medical Faculty; Infection
Hatay
Hatay
Türkiye
31040

Study participating centre
Mersin Universitesi Tip Fakultesi Hastanesi; Tibbi Onkoloji Birimi
Mersin
Mersin
Türkiye
33110

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

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

Study participating centre
Mississippi Center for Advanced Medicine
Madison
Mississippi
United States of America
39110

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
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes