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A study to evaluate overall health, physical activity and joint outcomes, in participants with severe or moderate hemophilia A without FVIII inhibitors on emicizumab prophylaxis

Submission date
12/05/2022

Registration date
13/05/2022

Last Edited
13/12/2023

Recruitment status
No longer recruiting

Overall study status
Ongoing

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
The aim of the study is to investigate the impact of emicizumab on overall health, physical activity and joint outcomes on eligible patients taking this treatment for a period of 36 months (about 3 years).

Emicizumab is an antibody that is manufactured in a laboratory. Emicizumab copies what the clotting factor (FVIII) does in the blood and increases the ability of your blood to clot. It is used for routine prophylaxis in haemophilia A to prevent or reduce the number of bleeding episodes.

Who can participate?
Participants will be aged between ≥ 13 and< 70 years with severe or moderate haemophilia A without inhibitors, who have previously received prophylaxis with factor VIII (FVIII)

The study will enrol up to 120 participants globally with severe or moderate haemophilia A without FVIII inhibitors, who have previously received prophylaxis with factor VIII (FVIII).

What does the study involve?
It is an open label study and all participants will receive treatment with emicizumab. This is given as an injection under the skin (subcutaneous injection).

What are the possible benefits and risks of participating?
Benefits:
Your 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.
Risks:
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.

Study Assessment Risks:
Some of these procedures take place more often than they would if patients were not taking part in this study. Please see the main or parent/guardian PISICFs for a list or risks.

Study Treatment:
Emicizumab will initially be given in a clinic with staff who are trained to monitor for and respond to any potential medical emergencies. With training, the participants or parent/legal guardian can administer injections between mandatory clinic visits at home.

Risks Associated with Emicizumab:
Side effects can be referred to in the main or parent/guardian PISICF due to the character count limit.

Unknown Risks:
It is possible that side-effects of emicizumab 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.

Pregnancy Prevention:
There may be a risk in exposing an unborn child to study drugs, and all risks are not known at this time. Women/girls of child bearing potential must take precautions to avoid exposing an unborn child to study drugs.

Participants will be asked to notify their study doctor or study staff should they experience any side effects during the study, and will be monitored throughout the study in order to minimise risks.

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

When is the study starting and how long is it expected to run for?
April 2022 to April 2027

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

Who is the main contact?
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Contact information

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05181618

Clinical Trials Information System (CTIS)
2020-005092-13

Integrated Research Application System (IRAS)
1004164

Central Portfolio Management System (CPMS)
50323

Protocol serial number

MO42623

Study information

Scientific Title
A multicenter, open-label phase IV study to evaluate overall health, physical activity, and joint outcomes, in participants aged ≥ 13 and < 70 years with severe or moderate hemophilia A without FVIII inhibitors on emicizumab prophylaxis

Acronym
MO42623 - Beyond The Bleed

Study objectives
• To evaluate the impact of emicizumab treatment on joint health and health-related quality of life (HRQoL) outcomes of participants with hemophilia A as well as their physical activity
• To evaluate the safety of emicizumab
• To evaluate the immune response to emicizumab

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/06/2022, London - West London & GTAC Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 1048 007; westlondon.rec@hra.nhs.uk), ref: 22/LO/0310

Primary study design
Interventional

Study design
Interventional randomized controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Hemophilia A is an inherited bleeding disorder in which blood does not clot normally. People with hemophilia A will bleed more than normal for example after an injury, surgery, or dental procedure.

Interventions
Cohort 1, Hemophilia A and Without Arthropathy: Emicizumab
Cohort 1 comprises participants with severe or moderate hemophilia A and with no synovitis and no osteochondral damage (Haemophilia Early Arthropathy Detection with Ultrasound [HEAD-US] score of 0) in all index joints. The emicizumab dosing regimen will be 3 milligrams per kilogram of body weight (mg/kg) subcutaneously (SC) once a week (QW) for 4 weeks followed by participant preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W) in agreement with the investigator.

Cohort 2, Hemophilia A and with Synovitis Only: Emicizumab
Cohort 2 comprises participants with severe or moderate hemophilia A and with synovitis (HEAD-US synovitis score of ≥1) in at least one joint and no osteochondral damage (HEAD-US bone and cartilage score of 0). The emicizumab dosing regimen will be 3 milligrams per kilogram of body weight (mg/kg) subcutaneously (SC) once a week (QW) for 4 weeks followed by participant preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W) in agreement with the investigator.

Cohort 3, Hemophilia A and with Osteochondral Damage: Emicizumab
Cohort 3 comprises participants with severe or moderate hemophilia A and with osteochondral damage (HEAD-US bone and cartilage score of ≥1) in at least one joint with any synovitis score. The emicizumab dosing regimen will be 3 milligrams per kilogram of body weight (mg/kg) subcutaneously (SC) once a week (QW) for 4 weeks followed by participant preference of one of the following maintenance regimens: 1.5 mg/kg QW, 3 mg/kg once every 2 weeks (Q2W), or 6 mg /kg once every 4 weeks (Q4W) in agreement with the investigator.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Hemlibra, emicizumab

Primary outcome(s)
1. Joint status over time based on centrally reviewed Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) scores with a specific focus on the synovitis score in participants with synovitis. At Screening (Day -28 to Day -1), Months 6, 12, 24 and 36
2. Clinical joint status over time based on the Hemophilia Joint Health Score (HJHS v2.1), excluding gait assessment. At Screening (Day -28 to Day -1), Months 6, 12, 24 and 36
3. Joint status at screening and month 36 based on centrally reviewed International Prophylaxis Study Group (IPSG) score (with MRI)
4. Number of problem joints and proportion of problem joints, defined as joints having chronic joint pain and/or limited range of movement due to compromised joint integrity (i.e., chronic synovitis and/or hemophilic arthropathy) with or without persistent bleeding, over time. At Months 6, 12, 24 and 36.
5. Number of target joint bleeds over time (target joints are defined as joints with >=3 bleeds occurring in the same joint during the last 24 weeks). Up to 36 months
6. HRQoL, as assessed through use of the Comprehensive Assessment Tool of Challenges in Hemophilia (CATCH) Questionnaire over time. At Baseline (Day 1), Months 3, 6, 12, 18, 24, and 36
7. Change in the level of physical activity during the study as measured with a wearable activity tracker (Fitbit). Until Month 36
8. Change in daily step count, active minutes metabolic equivalents of tasks (METs), moderate to vigorous physical activity (MVPA; as per activity tracker default categorization), and type of physical activities. Until Month 36
9. Change in the time and intensity level of physical activity as measured by the International Physical Activity Questionnaire Short Format (IPAQ-SF). At Baseline (Day 1), Months 3, 6, 12, 18, 24, and 36
10. Number of all bleeds (i.e., those treated and untreated with FVIII), treated bleeds, spontaneous bleeds, joint bleeds, treated joint bleeds, and target joint bleeds (i.e., bleed rate)

over time (ABR) as assessed through use of the Bleed and Medication Questionnaire (BMQ). Until Month 36
11. Participant and/or caregiver preference for emicizumab compared with previous FVIII regimen, as assessed through use of the Emicizumab Preference Survey (EmiPref) at month 6

Key secondary outcome(s)
Until 24 weeks (Safety Follow-up) after the final dose of emicizumab unless otherwise noted:
1. Incidence and severity of adverse events, with severity determined according to World Health Organization (WHO) toxicity scale
2. Incidence of thromboembolic events
3. Incidence of thrombotic microangiopathy
4. Incidence of severe hypersensitivity, anaphylaxis, and anaphylactoid events
5. Incidence and severity of injection-site reactions
6. Prevalence of anti-drug antibodies (ADAs) against emicizumab at baseline and incidence of ADAs against emicizumab during the study. At Baseline (Day 1), Months 6, 12, 24 and 36
7. Number and proportion of participants who develop anti-FVIII inhibitors (titer >=0.6 BU/mL) at specified timepoints. Up to 36 months

Completion date
20/04/2027

Eligibility

Key inclusion criteria
1. Age >=13 and <70 years at time of signing Informed Consent Form
2. Diagnosis of severe congenital hemophilia A (intrinsic FVIII level <1%) or moderate congenital hemophilia A (intrinsic FVIII level <=5%) if previously prescribed prophylaxis
3. A negative test for FVIII inhibitor (i.e., <0.6 BU) within 8 weeks of enrollment
4. Participants who completed successful immune tolerance induction (ITI) at least 5 years before screening are eligible, provided they have had no evidence of inhibitor recurrence (permanent or temporary) as may be indicated by detection of an inhibitor, FVIII half-life < 6 hours, or FVIII recovery < 66% since completing ITI
5. Participants who were on standard FVIII prophylaxis, defined as the regular administration of FVIII to prevent bleeding, for at least the last 24 weeks, can be enrolled regardless of the number of bleeds during this period
6. Adequate hematologic, hepatic and renal function
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception during the treatment period and for at least 24 weeks after the final dose of emicizumab

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
13 Years

Upper age limit
70 Years

Sex
All

Total final enrolment
14

Key exclusion criteria
1. Inherited or acquired bleeding disorder other than severe congenital hemophilia A (intrinsic FVIII level <1%) or moderate congenital hemophilia A (intrinsic FVIII level <=5%) without FVIII inhibitors who were previously prescribed prophylaxis for at least 24 weeks
2. Participants who have previously received emicizumab prophylaxis
3. Participants who had joint replacement, joint procedure, synovectomy or synoviorthesis less than 5 years ago, or participants who had joint replacement, joint procedure, synovectomy or synoviorthesis more than 5 years ago but are still experiencing pain in the joint (only the specific joint will be excluded from the study), or participants that plan to have joint replacement, joint procedure, synovectomy or synoviorthesis, or participants that are deemed suitable candidates for joint replacement, joint procedure, synovectomy or synoviorthesis at screening
4. Participants who have conditions other than hemophilia A that can affect joint health and structure (e.g., osteoarthritis) or with severely impaired mobility due to conditions other than hemophilia A
5. Participants with reduced bone mineral density defined as clinically relevant vitamin D deficiency
6. Participants with pre-existing cardiovascular disease not receiving controlled and targeted medication or in a stable condition
7. Participants not eligible for MRI
8. History of illicit drug or alcohol abuse within 48 weeks prior to screening
9. Participants who are at high risk for thrombotic microangiopathy (TMA)
10. Previous (within the last 12 months) or current treatment for thromboembolic disease (with the exception of previous catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing) or signs of thromboembolic disease
11. Other conditions (e.g., certain autoimmune diseases) that may currently increase the risk of bleeding or thrombosis
12. History of clinically significant hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection
13. Planned surgery during the emicizumab loading dose phase. Surgeries in participants on emicizumab from Week 5 onwards are allowed
14. Known HIV infection not controlled by medication
15. Concomitant disease, condition, significant abnormality on screening evaluation or laboratory tests, or treatment that could interfere with the conduct of the study, or that would in the opinion of the investigator, pose an additional unacceptable risk in administering study drug to the participant
16. Receipt of any of the following:
16.1 An investigational drug to treat or reduce the risk of hemophilic bleeds within 5 half-lives of last drug administration at screening
16.2 A non-hemophilia-related investigational drug within last 30 days or 5 half-lives at screening, whichever is shorter
16.3 Any other investigational drug currently being administered or planned to be administered

17. Inability to comply with the study protocol
18. Pregnant or breastfeeding, or intending to become pregnant during the study

Date of first enrolment
14/01/2022

Date of final enrolment
04/12/2023

Locations

Countries of recruitment
United Kingdom

England

Brazil

Canada

Germany

Hungary

Ireland

Italy

Morocco

Russian Federation

Serbia

Spain

Switzerland

Tunisia

Türkiye

Study participating centre
Manchester Royal Royal Infirmary
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Study participating centre
St Thomas' Hospital
Westminster Bridge Road
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Sponsor information

Organisation
F. Hoffmann-La Roche Ltd (Switzerland)

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?
HRA research summary			26/07/2023	No	No