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Study to investigate the effectiveness of emicizumab under real-world conditions in paediatric, adolescent, adult and elderly participants with haemophilia A with and without Factor VIII (FVIII) inhibitors

Submission date
14/01/2022

Recruitment status
No longer recruiting

Registration date
09/02/2022

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

Haemophilia A is an inherited disorder in which the blood does not clot due to a deficiency of clotting factor VIII (FVIII; a protein that help the blood to clot). Common signs of hemophilia A include easy bruising, prolonged bleeding after trauma or surgery, spontaneous bleeding into joints, muscles or soft tissues, and intracranial haemorrhage (bleeding inside the skull). The severity of haemophilia A is directly related to the FVIII activity. There is no cure for haemophilia A and those with the disorder require life-long treatment.

Treatment involves replacing the missing clotting factor. Factor VIII can be obtained from blood donations but is now usually created artificially in a lab. This is called recombinant factor VIII. Replacement therapy may be administered as regular continuous treatment or as episodic (on-demand) treatment given at the time of bleeding. People with severe haemophilia A usually receive prophylactic treatment to help prevent bleeding episodes and complications. One of the most severe treatment-related complications that occurs in some people is the development of certain proteins that neutralise FVIII called FVIII inhibitors. As FVIII can no longer be used to control bleeding, people with inhibitors are treated with bypassing agents (BPAs, treatments that “bypass” the need for clotting factor treatment) such as recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrate (aPCC). This type of treatment is short-acting and needs to be administered frequently.

Emicizumab (Hemlibra®) is a drug that was approved by health authorities for the routine prophylaxis of bleeding episodes in adults, adolescents, and children with Haemophilia A with factor VIII inhibitors and for severe Haemophilia A without factor VIII inhibitors. The aims of this study are to:

1. To find out the long-term effectiveness of emicizumab prophylaxis in actual conditions in participants with congenital (present from birth) Haemophilia A. Two groups of participants will be observed: participants with severe Haemophilia A without FVIII inhibitors and participants with Haemophilia A (any severity) with FVIII inhibitors

2. To determine the percentage of participants with zero treated bleeds
3. To determine the annualised bleeding rate and the percentage of participants with zero bleeds as compared to those with treated spontaneous bleeds, treated joint bleeds and treated target joint (one particular joint has recurrent bleeding) bleeds
4. To assess the type, dosing, and frequency of haemostatic medication (medicines to stop bleeding) besides emicizumab used to treat bleeding events or for other purposes
5. To assess the participants' perceived physical and mental health over time using the health-related quality of life questionnaires which are specific to different age groups such as children, adolescents, adults, and elderly
6. To determine the preferred dosing regimen for emicizumab prophylaxis such as once a week, every 2 weeks, every 4 weeks etc
7. To determine the blood levels of emicizumab in actual conditions
8. To assess the health of joints using a scale known as the Hemophilia Joint Health Score
9. To assess descriptively the number and reasons for invasive surgical procedures
10. To assess the usage of pain medications
11. To assess the disability caused by haemophilia A in performing the functions of any occupation
12. To evaluate the participants' use of health resources related to Haemophilia A by assessing the number of contacts to site (visits and telephone calls), unscheduled visits at site, number of emergency room (ER) visits, number of hospitalisations related to Haemophilia A, including length of stay, and number of physiotherapies received
13. To find out the frequency of newly occurring FVIII inhibitors in participants undergoing Emicizumab prophylaxis and additionally treated with FVIII
14. To find out the level of FVIII inhibitors over time
15. To find out the percentage of participants receiving immune tolerance induction (ITI, a process that helps to achieve permanent elimination of the inhibitors) and the frequency of FVIII injections for ITI
16. To assess the occurrences of side effects in participants of all age groups.
17. To determine the occurrence and significance of neutralizing anti-drug antibodies (ADAs, proteins that prevent the drug activity) under actual conditions in all participants

Who can participate?
Participants of any age with congenital haemophilia A with FVIII inhibitors or severe haemophilia A without FVIII inhibitors.

What does the study involve?
This study is being conducted in Germany and Switzerland at about 25 specialised haemophilia centres. The duration of the study is 5 years. Participants will be observed for a minimum of 1 year to a maximum of 5 years.
During the study, the participants' regular visits are recorded by the study doctor in a standardised form either on paper or electronically. In addition, participants will be asked to fill out two questionnaires about their quality of life at the beginning of the data collection and every 6 months. The contents of the questionnaire do not go beyond the information requested in the context of normal medical practice. The questionnaires will be handed out to participants by the doctor during a routine visit with a request for an answer. Filling out a questionnaire may take about 5-10 minutes. The joint health of the participants will be documented once a year at the beginning of the data collection and during the study period.
The type and duration of treatment that the participants are receiving will not get influenced by study participation.
Participants may also be asked to keep a bleeding diary to record important information about each bleeding episode. The following data will be collected from the bleeding diary:
1. Place of bleeding

2. Type of bleeding
3. Reason for bleeding
4. Time of each individual bleeding (day of onset of bleeding)
5. Symptoms of bleeding
6. Treatment of bleeding (medicines, onset and end, dose) and other treatments directly related to bleeding (e.g., additional painkillers, if consumed, due to bleeding)
7. Number of bleedings treated in the last 6 months before the first hemlibra® administration

The following information will be collected from participants' medical records during the course of the study:
1. Body weight if there are changes
2. Data about haemophilia and the medicines given to prevent or treat bleeding
3. Data on treated bleeding from bleeding diary
4. Details of treatment with Hemlibra® (dosage, frequency) and changes, if any
5. Data on other conditions and/or other medicines participants may be taking
6. Details of the use of medical services due to haemophilia (frequency of contacts with the haemophilia centre, frequency of hospitalisations/stays in the intensive care unit and frequency of prescriptions for physiotherapy)
7. Possible occupational disability due to haemophilia, if any
8. Results of the questions on quality of life
9. Data of joint health, once a year
10. Results of blood tests
11. Data on side effects, illnesses, accidents, injuries, and other events affecting the health of participants during and after emicizumab treatment

In order to fully record possible side effects, a doctor will document events that occur from the first dose of emicizumab to the end of the observation period of this study. Participants who discontinue emicizumab will be monitored for adverse events for a period of 6 months.

What are the possible benefits and risks of participating?
Participants will not receive any benefit from participating in this study, but the information that is learned from this study may help researchers and doctors to learn more about haemophilia A in general and other people who have a similar medical condition may benefit from the results of such research in the future. There are no risks from participating in the study as it is observational.

Where is the study run from?
Roche (Germany)

When is the study starting and how long is it expected to run for?
February 2019 to January 2025

Who is funding the study?
Roche (Germany)

Who is the main contact?
global.trial_information@roche.com

Contact information

Type(s)

Public

Contact name
Ms Medical Information

Contact details
Emil-Barell-Str. 1
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
ML40914

Study information

Scientific Title
Non-interventional study to investigate the effectiveness of emicizumab under real-world conditions in pediatric, adolescent, adult and elderly patients with hemophilia A with and without FVIII inhibitors

Acronym
EMIIL

Study objectives
The purpose of this study is to evaluate the long-term effectiveness of emicizumab prophylaxis in pediatric, adolescent, adult, and elderly patients with hemophilia A with and without FVIII inhibitors under real-world conditions.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/05/2019, Ethics Committee of Rhenish Friedrich Wilhelm University of Bonn (Sigmund-Freud-Str. 25, 53127 Bonn, Germany; +49 228 287 51931; ethik@uni-bonn.de), ref: 151 /19

Study design
Single-arm two-cohort prospective multicentre non-interventional study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Haemophilia A

Interventions
Cohort A: The participants with congenital severe haemophilia A without Factor VIII (FVIII) inhibitors who are undergoing emicizumab treatment as described in the Hemlibra® (Emicizumab) summary of product characteristics (SPC), will be observed and asked to complete questionnaires every 6 months at the study centre until the end of study if emicizumab treatment is not discontinued (maximum up to 5 years).

Cohort B: The participants with congenital haemophilia A (any severity) with FVIII inhibitors who are undergoing emicizumab treatment as described in the Hemlibra® (Emicizumab) SPC, will be observed and asked to complete questionnaires every 6 months at the study centre until the end of study if emicizumab treatment is not discontinued (maximum up to 5 years).

Intervention Type
Drug

Phase
Not Applicable

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

Primary outcome(s)
Annualized bleeding rates (ABRs) of treated bleeds estimated using nature and number of treated bleeds in the past 24 weeks prior to the emicizumab treatment, derived from participant' s files and treatment diaries from baseline until the end of the study (up to 5 years)

Key secondary outcome(s))
1. Percentage of participants with zero treated bleeds estimated using nature and number of treated bleeds in the past 24 weeks prior to the emicizumab treatment, derived from participant' s files and treatment diaries from baseline until the end of the study (up to 5 years)
2. ABRs of treated spontaneous bleeds, treated joint bleeds, treated target joint bleeds estimated using nature and number of treated bleeds in the past 24 weeks prior to the emicizumab treatment, derived from participant's files and treatment diaries from baseline until the end of the study (up to 5 years)
3. Percentage of participants with zero treated spontaneous bleeds, treated joint bleeds, treated target joint bleeds estimated using nature and number of treated bleeds in the past 24 weeks prior to the emicizumab treatment, derived from participant's files and treatment diaries from baseline until the end of the study (up to 5 years)
4. Number of doses and frequency of haemostatic medication besides emicizumab used to treat bleeding events or for other purposes, derived from participant's files and treatment diaries from baseline until the end of the study (up to 5 years)
5. Percentage of participants with different dosing regimens of emicizumab, derived from

participant’s files and treatment diaries from screening up to the end of the study (up to 5 years)
6. Number of invasive surgical procedures, derived from participant’s files and treatment diaries from day 1 up to the end of the study (up to 5 years)
7. Percentage of participants that used pain medication, derived from participant’s files and treatment diaries from day 1 up to end of study (up to 5 years)
8. Percentage of participants with occupational disability related to haemophilia A, derived from participant’s files and treatment diaries from day 1 up to the end of the study (up to 5 years)
9. Number of events of using health resources (number of contacts to the site, unscheduled visits at the site, number of emergency room (er) visits, number of hospitalizations related to haemophilia a, number of physiotherapies received), derived from participant’s files and treatment diaries from day 1 up to end of study (up to 5 years)
10. Number of participants with newly occurring FVIII inhibitors under emicizumab prophylaxis and additionally treated with FVIII in cohort A, derived from participant’s files and treatment diaries from screening until the end of the study (up to 5 years)
11. Level of FVIII inhibitors over time, derived from participant’s files and treatment diaries from screening until the end of the study (up to 5 years)
12. Percentage of participants receiving parallel immune tolerance induction (ITI) inhibitors who develop new FVIII inhibitors, derived from participant’s files and treatment diaries from screening until the end of the study (up to 5 years)
13. Percentage of participants with serious adverse events, non-serious adverse events, and adverse events of special interest, derived from participant’s files and treatment diaries from screening up to the end of the study (up to 5 years)
14. Percentage of participants experiencing thrombotic microangiopathies and thrombotic events (TES), derived from participant’s files and treatment diaries from screening until the end of the study (up to 5 years)
15. Percentage of participants with anti-drug antibodies at baseline and after initiation of study treatment indirectly evident by functional assays and exclusion of non-adherence from screening until the end of the study (up to 5 years)

Completion date
31/01/2025

Eligibility

Key inclusion criteria
1. Participants of any age with congenital severe haemophilia A with or without FVIII inhibitors
2. Participants undergoing treatment with emicizumab according to Summary of Product Characteristics (SPC) (start of treatment with emicizumab maximum 3 months prior to study entry)
3. Must sign informed consent by the legal representative or participant or both, as required
4. Selection criteria for Cohort A include participants diagnosed with severe congenital haemophilia A (<1% FVIII activity) and no present FVIII inhibitor at the start of emicizumab treatment, patients who completed successful ITI before the start of Emicizumab treatment are eligible.
5. Selection criteria for Cohort B include participants diagnosed with congenital haemophilia A (any severity) with FVIII inhibitor activity at the start of emicizumab treatment or ongoing ITI at the start of emicizumab treatment

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Sex
Male

Key exclusion criteria
1. Participants having bleeding disorder other than congenital haemophilia A
2. Treatment with emicizumab outside of the SPC at study entry
3. Any contraindication for treatment with emicizumab according to current SPC
4. Current participation in an interventional study

Date of first enrolment
20/01/2020

Date of final enrolment
23/01/2024

Locations

Countries of recruitment
Germany

Switzerland

Study participating centre
Medizinische Hochschule Hannover
Carl-Neuberg-Str 1
Hannover
Germany
30625

Study participating centre
Universitätsklinikum Hamburg-Eppendorf
Martinistr. 52
Hamburg
Germany
20246

Study participating centre
Goethe-Universität Frankfurt
Theodor-W. Adorno-Platz 1

Frankfurt
Germany
60323

Study participating centre
Justus-Liebig-Universität Gießen-Marburg
Ludwigstr. 23
Giessen
Germany
35390

Study participating centre
MVZ Werlhof-Institut
Werlhof-Institut für Hämostaseologie GmbH, Schillerstr. 23
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Germany
30159

Study participating centre
Universitätsklinikum Regensburg Abt. für pädiatrische Hämatologie, Onkologie und Stammzelltransplantation
Franz Josef Strauss-Allee 11
Regensburg
Germany
93053

Study participating centre
HZRM Hämophilie-Zentrum Rhein Main GmbH
Hessenring 13A
Moerfelden Walldorf
Germany
64546

Study participating centre
Charité – Universitätsmedizin
Augustenburger Platz 1
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13353

Study participating centre
UK Homburg
Universität des Saarlandes
Ringstraße 52
Homburg
Germany
66421

Study participating centre
MVZ Labor Dr. Reising-Ackermann und Kollegen Zentrum für Blutgerinnungsstörungen
Struempellstrasse 40
LEIPZIG
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04289

Study participating centre
Uniklinik Jena
Universitätsklinikum Jena
Klinik für Innere Medizin II
Abteilung Hämatologie und Internistische Onkologie
Am Klinikum 1
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Germany
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Study participating centre
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04103

Study participating centre
SRH Kurpfalzkrankenhaus Heidelberg GmbH
Bonhoefferstraße 5
Heidelberg
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69123

Study participating centre

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Bonn
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53127

Study participating centre
Kinderspital Zürich
Steinwiesstrasse 75
Zürich
Switzerland
8032

Study participating centre
Hôpitaux Universitaires de Genève
Rue Gabrielle-Perret-Gentil 4
Genève
Switzerland
1205

Study participating centre
Universitäts-Kinderspital beider Basel
Spitalstrasse 33
Basel
Switzerland
4056

Study participating centre
EOC (Istituto Pediatrico della Svizzera Italiana)
Viale Officina 3
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6500

Study participating centre
CHUV (Unité d'Hémato-Oncologie Pédiatrique)
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Lausanne
Switzerland
1011

Study participating centre
Inselspital, Universitätsspital Bern
Freiburgstrasse 15
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Switzerland
3010

Sponsor information

Organisation
Roche (Germany)

ROR
https://ror.org/00sh68184

Funder(s)

Funder type
Industry

Funder Name
Roche

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co., Roche Holdings, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study are not expected to be made available due to participant-level data not being a regulatory requirement.

IPD sharing plan summary

Not expected to be made available

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