NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**LONG-TERM NON-INTERVENTIONAL SAFETY STUDY OF EMICIZUMAB TREATMENT IN PATIENTS WITH MODERATE HAEMOPHILIA A AND SEVERE BLEEDING PHENOTYPE (STUDY BO44691, PASS)**
PROTOCOL NUMBER:	BO44691
VERSION NUMBER:	V2.0
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
AUTHOR:	[redacted] PhD, [redacted] F. Hoffmann - La Roche Ltd, Basel, Switzerland [redacted] Phone: [redacted]
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
15-Nov-2023 11:26:29	[redacted]	[redacted]
15-Nov-2023 11:26:47	Company Signatory	[redacted]

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ACTIVE SUBSTANCE:	B02BX06: Emicizumab
PRODUCT REFERENCE NUMBER:	EMEA/H/C/004406
PROCEDURE NUMBER{S}:	NA
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The study aims to evaluate the long-term safety profile (with focus on thromboembolic [TE] events) of emicizumab in patients with moderate congenital Haemophilia A (1% ≤ Factor VIII [FVIII] ≤ 5%), without FVIII inhibitors and with severe bleeding phenotype, who are exposed to emicizumab in real-world settings. The primary objective for this study is to determine the incidence of TE events. The secondary objectives for this study are: 1. To determine the incidence of serious adverse events (SAEs). 2. To determine the incidence of thrombotic microangiopathy (TMA) events. 3. To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis. 4. To characterise the risk profile in terms of pre-defined risk factors of TE events in the patient population. 5. To describe characteristics of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis (e.g., diagnosis and symptoms). 6. To characterise the impact of the prior use of FVIII prophylaxis on the incidence of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis.

COUNTRIES OF STUDY POPULATION:	Including, but not limited to the European region
MARKETING AUTHORISATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
MAH CONTACT PERSON:	Ms. [redacted] c/o Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualised Bleed Rate
ADRs	Adverse Drug Reactions
AE	Adverse Event
aPCC	Activated Prothrombin Complex Concentrates
ATHN	American Thrombosis and Hemostasis Network
BMI	Body Mass Index
CBDR	Canadian Bleeding Disorders Registry
CDM	Common Data Model
CHESS	Canadian Hemophilia Surveillance System
CHMP	Committee For Medicinal Products For Human Use
CI	Confidence Interval
CNHP	Czech National Haemophilia Programme
CRF	Case Report Form
DMP	Data Management Plan
EC	European Commission
ENCePP	European Network Of Centres For Pharmacoepidemiology And Pharmacovigilance
EU	European Union
EU PAS	European Post-Authorisation study
EUHASS	European Haemophilia Safety Surveillance
FIXa	Activated Factor IX
FVIII	Factor VIII
FX	Factor X
GPP	Good Pharmacoepidemiology Practice
HA	Haemophilia A
HRQoL	Health-Related Quality Of Life
ICD	International Classification Of Diseases
IEC	Independent Ethics Committee
IR	Incidence Rate
IRB	Institutional Review Board
ITT	Intention To Treat
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary For Regulatory Activities
NHD	National Haemophilia Database
NI	Non-Interventional
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report

Abbreviation	Definition
PLD	Patient-Level Data
PSUR	Periodic Safety Update Report
PY	Person-Years
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SOP	Standard Operating Procedure
TE	Thromboembolic
TMA	Thrombotic Microangiopathy
UKHCDO	UK Haemophilia Centre Doctors Organisation
US	United States
WBDR	World Bleeding Disorders Registry

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3. ABSTRACT/SYNOPSIS

TITLE:	**LONG-TERM NON-INTERVENTIONAL SAFETY STUDY OF EMICIZUMAB TREATMENT IN PATIENTS WITH MODERATE HAEMOPHILIA A AND SEVERE BLEEDING PHENOTYPE (STUDY BO44691, PASS)**
PROTOCOL NUMBER:	BO44691
VERSION NUMBER:	2.0
DATE OF SYNOPSIS:	November 2023
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
SCIENTIFIC RESPONSIBLE:	[redacted]
MAIN AUTHOR:	[redacted]
PHASE:	IV, non-interventional study
INDICATION:	Moderate congenital Haemophilia A (1% ≤ FVIII ≤ 5%), without FVIII inhibitors and with severe bleeding phenotype
MARKETING AUTHORISATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

Rationale and Background

Haemophilia A (HA) is a congenital form of haemophilia causing a lack of coagulation factor VIII (FVIII). Bleeding often occurs in joints and can result in severely damaged and deformed joints; it can also occur in any other part of the body and can be life-threatening.

The goal of haemophilia treatment is to reduce the risk of bleeding and other complications of the disorder. Haemophilia treatment of more severe cases have traditionally relied on FVIII infusions that often poses a significant burden on the patient and even during prophylactic treatment patients can experience a high rate of bleeding events.

Emicizumab (Hemlibra®) is a recombinant, humanised, bispecific monoclonal antibody that mimics the function of activated FVIII without being structurally similar, meaning that emicizumab is not linked to the development or is affected by the presence of FVIII inhibitors. The use of subcutaneous (SC) injection as the route of administration also results in significantly lower patient burden of treatment.

In the European Union (EU), the marketing authorisation holder (MAH) submitted an extension of indication for Hemlibra to include routine prophylaxis of bleeding episodes in patients with congenital HA without FVIII inhibitors who have moderate disease (1% ≤ FVIII ≤ 5%) with severe bleeding phenotype.

On 15 December 2022, the committee for medicinal products for human use (CHMP) issued a positive opinion for this new extension of indication; European commission (EC) decision was received on 23 January 2023.

To fulfil the resultant category 3 post-authorisation safety study (PASS) regulatory commitment in the EU, the MAH proposed a multi-registry PASS study to characterise the important potential risk of thromboembolic (TE) events (not associated with activated prothrombin complex concentrates [aPCC] exposure) specifically and inform on the long-term safety profile of emicizumab in the new patient population.

Research Question and Objectives

The aim of the study is to evaluate the long-term safety profile of emicizumab in patients with moderate congenital HA (1% ≤ FVIII ≤ 5%) without FVIII inhibitors and with severe bleeding phenotype and who are exposed to emicizumab in real-world settings, with a specific focus on TE events.

The primary objective for this study is to determine the incidence of TE events.

The secondary objectives for this study are:

1. To determine the incidence of serious adverse events (SAEs).
2. To determine the incidence of thrombotic microangiopathy (TMA) events.
3. To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis.
4. To characterise the risk profile in terms of pre-defined risk factors of TE events in the patient population.

5. To describe characteristics of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis (e.g., diagnosis and symptoms).

6. To characterise the impact of the prior use of FVIII prophylaxis on the incidence of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis.

Study Design

This non-interventional (NI) PASS is a multi-country, registry-based, longitudinal cohort study based on secondary use of data collected for patients of all ages with moderate congenital HA, without FVIII inhibitors and with severe bleeding phenotype, treated with emicizumab

Patients will be assessed for inclusion during the cohort entry period, this will last from market authorisation of emicizumab for use among moderate patients without inhibitors in each participating country until approximately Q4 2026.

Patients will be followed from the index date, which will be the date of emicizumab treatment initiation for each patient during the cohort entry period, until discontinuation of emicizumab, death, end of observation (due to loss to follow-up, emigration, or disenrollment from the registry), a maximum of 5 years, or end of study period (anticipated Q4 2030), whichever occurs first.

Data Sources

This PASS will use data routinely collected within registries containing haemophilia patients primarily but not limited to the European region. The specific registries considered for this study were determined in a feasibility study that was conducted to identify the most appropriate data sources for this study. Participation of each data source is conditional to contracting. The considered data sources are listed below:

- UK National haemophilia database (United Kingdom)
- FranceCoag registry / Reseau FranceCoag (France)
- HemoNED (Netherlands)
- American Thrombosis and Hemostasis Network dataset (United States)
- World Bleeding Disorders Registry (Multi-country)
- Canadian Bleeding Disorders Registry (Canada)

Population

Inclusion criteria:

- Diagnosis of congenital HA;
- Moderate disease classification (1% ≤ FVIII ≤ 5%);
- Severe bleeding phenotype;

The above-mentioned inclusion criteria will ensure that the patient is eligible for the extended indication of emicizumab.

In addition, the patient will have to fulfil the following criteria:

- Initiation of emicizumab treatment during the cohort entry period;
- Information on previous HA outcomes and HA treatments approximately 12 months prior to the index date. In case HA diagnosis occurred within 12 months of the index date, the required lookback period will be shortened to time from HA diagnosis to index date. Anamnestic information capturing historic events but entered in the registry database less than 12 months before the index date will be considered as long as they were recorded prior to the index date;
- Information on risk factors of TE events (e.g., medical comorbidities, treatments and demographic characteristics) approximately 12 months prior to the index date. If the patient is below 1 year of age, the lookback period will be shortened to birth until index date. Anamnestic information capturing historic events but entered in the registry database less than 12 months before the index date will be considered as long as they were recorded prior to the index date;
- Signed the informed consent form where required by local regulations.

Exclusion criteria:

- Development of FVIII inhibitors any time before the index date;
- Treatment with emicizumab at any time before the index date.

Variables

Primary Safety Variables

The primary variables for this study are as follows:

- TE events

Secondary Variables

The secondary variables for this study are as follows:

- SAEs
- TMA events
- Serious systemic hypersensitivity reactions, including anaphylaxis
- Demographic characteristics
- Time since diagnosis of congenital HA
- Prior treatments for haemophilia
- HA medical history
- Concomitant medications
- Other medical history and concurrent conditions
- Risk factors for TE events.

Study Size

Projected real-world study size based on feasibility study and existing literature on prevalence of inhibitors and moderate HA population, indicates ~202 patients newly

exposed to emicizumab can be captured with a total study population of 3000 moderate HA patients, within the cohort entry period.

Study size estimations were done via simulations to assess whether the real-world estimate is adequate for the primary objective of estimating the crude incidence rate (IR) of 1st TE events by varying sample size targets, expected event rates and threshold value for 95% Clopper-Pearson confidence interval (CI). Simulations were run to calculate expected accuracy defined as the probability that the CI of the crude IR does not exceed an upper threshold.

Approximately 200 emicizumab exposed patients across all study countries will be necessary with an average follow-up of 4 years for each patient, to achieve 88% probability that the 95% Clopper-Pearson CI of the crude IR does not exceed a threshold value of one event per 100 person-years (PY). This assumes an expected crude IR of TE events of 0.15 events per 100 PY.

Data Analysis

This study does not include any formal comparison and is purely descriptive. A common data model (CDM) will be used to create aggregated data, either by the data source or by IQVIA. This CDM will define the level of aggregation and minimum information required to enable the statistical analysis of the study objectives. The aggregated datasets will be pooled for the statistical analysis.

For the primary objective, crude IRs for 1st TE events during the follow-up period per 100 PY will be described. For the calculation of crude IRs, the denominator will be the pooled person-time of all the patients within the cohort and the numerator will be all first events occurring during the follow-up period. In addition of crude IRs, incidence proportions will also be calculated.

For the analysis of secondary objectives 1, 2, 3, 4 and 6, crude IRs per 100 PY will be calculated and for secondary objective 5, descriptive tabulations will be done for SAE and TE events.

For secondary objective 1, 2, 3 the numerators will be the number of first occurrences of any SAE, 1st TMA events and 1st serious systemic hypersensitivity reaction events during the follow-up period, respectively. The denominators for the crude IRs will be the pooled person-time. For secondary objective 4, the events will be counted for each category/stratum of relevant pre-defined risk factors of TE events, to yield crude IRs of TE per category/stratum. For analysis of secondary objective 5, characteristics of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis (e.g., diagnosis and symptoms), will be tabulated. In addition, time to the 1st

TE events, SAE, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis events will be described by Kaplan-Meier curves. For analysis of secondary objective 6, calculation of crude IR and crude incidence proportion of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis, will be calculated, and tabulated for FVIII prophylaxis use (yes/no) prior to emicizumab treatment.

All crude IRs will be presented with 95% CI. For continuous variables, the number of observations, mean, standard deviation, median, lower (1st) and upper (3rd) quartiles, interquartile range (IQR), minimum, maximum, as well as 5th and 95th percentiles will be presented. For categorical variables, the numbers, and percentages of observations for each of the categories will be presented. Numbers and percentages of missing values will be presented.

Milestones

First Data Extraction:

The first data extraction is the date from which the variables used for the analysis as per protocol start to be extracted. The planned first data extraction is approximately 1 year after study launch. The planned first data extraction is Q2 2025.

Last Data Extraction:

The last data extraction is the date after the last included patient has completed their minimum follow-up of 4 years. The planned last data extraction date is Q4 2030.

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: None

5. MILESTONES

The final study report will be submitted as a standalone procedure in the EU PAS registry. The interim reports will be included in the Periodic Safety Update Report (PSUR) / Periodic Benefit Risk Evaluation Report (PBRER).

Milestone	Planned Date
Registration of protocol in the EU PAS register	Q1 2024
First Data Extraction	Q2 2025
Second Data Extraction	Q2 2027
Last Data Extraction	Q4 2030
First interim report	Q4 2025
Second interim report	Q4 2027
Final report of study results (CSR)	Q2 2031
Registration of the results in the EU PAS register	Q3 2031

6. RATIONALE AND BACKGROUND

6.1. BACKGROUND

Haemophilia A (HA) is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with congenital HA have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Franchini and Mannucci, 2013; Mannucci and Tuddenham, 2001). Three severity levels of the disease are distinguished based on the percentage of the normal FVIII plasma procoagulant levels, mild (>5% - <40%), moderate (1% - 5%), and severe (<1%) (White et al., 2001).

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of congenital HA include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial haemorrhage, leading to frequent bleeding events with the sequelae of musculoskeletal complications, such as arthropathy, local functional deficits, haemorrhagic shock, neurocognitive defects, or even death (Stonebraker et al., 2020). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al., 2009).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimise bleeding events and complications (Manco-Johnson et al., 2007). Since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for patients with congenital HA (Kingdon and Lundblad, 2002). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate nadir FVIII levels of 1%,

whereas others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnström et al., 2004; Collins et al., 2010). Current standard prophylactic regimens commonly use infusion therapy administered 3 times weekly; other regimens require every other day administration, depending on the patient's needs (Shapiro, 2013). Furthermore, the risk of bleeding is not directly proportional to the severity of the disease as measured by the percentage of the normal FVIII plasma procoagulant levels. Thus, a subset of patients with non-severe disease severity have a severe bleeding phenotype that require prophylactic treatment (den Uijl et al., 2014).

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%−30% of patients with severe congenital HA and in 3%−13% of those with moderate or mild disease (Franchini and Mannucci, 2013). The only haemostatic options previously available were pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents") (Srivastava et al., 2020).

Hemlibra (also known as emicizumab, ACE910, and RO5534262) is a recombinant, humanised, bispecific, immunoglobulin G4 monoclonal antibody (IgG4) that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX). In patients with congenital HA, Hemlibra bridges FIXa and FX to restore the function of missing activated FVIII that is needed for effective haemostasis. In patients with congenital HA, haemostasis can be restored irrespective of the presence of FVIII inhibitors, as Hemlibra shares no sequence homology with FVIII. In addition, Hemlibra offers the subcutaneous (SC) administration, removing the need for venous access. The recommended dose for emicizumab is 3 mg/kg of bodyweight weekly during the first 4 weeks. Maintenance dosage from week 5 and onwards is either 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg of bodyweight every 4 weeks. Because of the possibility of markedly extended dosing intervals, to once weekly or even less frequently, this compound dramatically change the treatment of patients with congenital HA with and without FVIII inhibitors who need effective, safe, and convenient prophylactic therapy.

Hemlibra received a marketing authorisation (MA) valid throughout the EU on 23 February of 2018 for the indication: routine prophylaxis of bleeding episodes in patients with congenital HA with FVIII inhibitors. On 31 January of 2019, the EU committee for medicinal products for human use (CHMP) adopted a favourable opinion on the expansion of the indication of Hemlibra to patients with severe congenital HA without FVIII inhibitors. Hemlibra can be used in all age groups.

6.2. RATIONALE

The marketing authorisation holder (MAH) submitted extension of indication for Hemlibra to include routine prophylaxis of bleeding episodes in patients with congenital HA without FVIII inhibitors who have moderate disease (1% ≤ FVIII ≤ 5%) with severe bleeding phenotype.

On 15 December 2022, the CHMP issued a positive opinion for this new extension of indication; the European Commission (EC) decision was received on 23 January 2023.

To fulfil the category 3 post-authorisation safety study (PASS) regulatory commitment in the EU, the MAH proposed a multi-registry, non-interventional (NI) PASS to characterise the important potential risk of thromboembolic (TE) events (not associated with aPCC exposure) specifically and inform on the long-term safety profile of emicizumab in the new patient population.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. RESEARCH QUESTION

The aim of the study is to evaluate the long-term safety profile of emicizumab in patients with moderate congenital HA (1% ≤ FVIII ≤ 5%) without FVIII inhibitors and with severe bleeding phenotype and who are exposed to emicizumab in real-world settings, with a specific focus on TE events.

7.2. OBJECTIVES

The primary objective for this study is to determine the incidence of TE events.

The secondary objectives for this study are:

1. To determine the incidence of serious adverse events (SAEs).
2. To determine the incidence of thrombotic microangiopathy (TMA) events.
3. To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis.
4. To characterise the risk profile in terms of pre-defined risk factors of TE events in the patient population.
5. To describe characteristics of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis (e.g., diagnosis and symptoms).
6. To characterise the impact of the prior use of FVIII prophylaxis on the incidence of TE events, SAEs, TMA events, and serious systemic hypersensitivity reactions, including anaphylaxis.

8. RESEARCH METHODS

8.1. STUDY DESIGN

This is a NI, multi-country, registry-based PASS, longitudinal cohort study based on secondary use of data collected for patients of all ages with moderate congenital HA, without FVIII inhibitors and with severe bleeding phenotype, treated with emicizumab,

The data sources will include registries containing haemophilia patients, primarily based in the European region, but also data sources in the US, Canada and Australia are considered. Data collection will focus on secondary data routinely collected within the registries prior to and after patients initiate treatment with emicizumab. The data sources under consideration are listed in section 8.4. The data will be extracted from the registries annually and pooled to a common data model (CDM) to perform pooled analyses. The planned first data extraction is approximately 1 year after registration of the protocol in the EU PAS register, the study launch. The last data extraction will the date after the last included patient has completed their minimum follow-up of 4 years, Q4 2030. Based on this, the final study report will be submitted as a standalone document in the EU PAS registry. Interim reports will be included in the PSUR/PBRER.

The aim of the study is to include approximately 200 patients who will be followed for a minimum of 4 years from the initiation of emicizumab treatment. According to previous clinical data, this follow-up time will be adequate to observe potential adverse events (AEs) and specifically TE events in the enrolled population (see section 8.6. for details). The overall study duration is expected to last a minimum of 6 years considering a 2-year period from approval of protocol until the end of patient inclusion. However, the overall length of study period will be dependent on MA of emicizumab for moderate patients without FVIII inhibitors. The study length may be adapted to each participating country, and, if needed, the study period may be amended to achieve the targeted sample size (see section 8.5. for details).

Data extracted from the registries will include data that pertains to haemophilia diagnosis, haemophilia disease and treatment history, emicizumab treatment, patient's demographic characteristics, ongoing and previous medication use (whether related to haemophilia or not), and a list of TE risk factors (see section 8.3. for details).

For an overview of the study design and assessment periods see Figure 1.

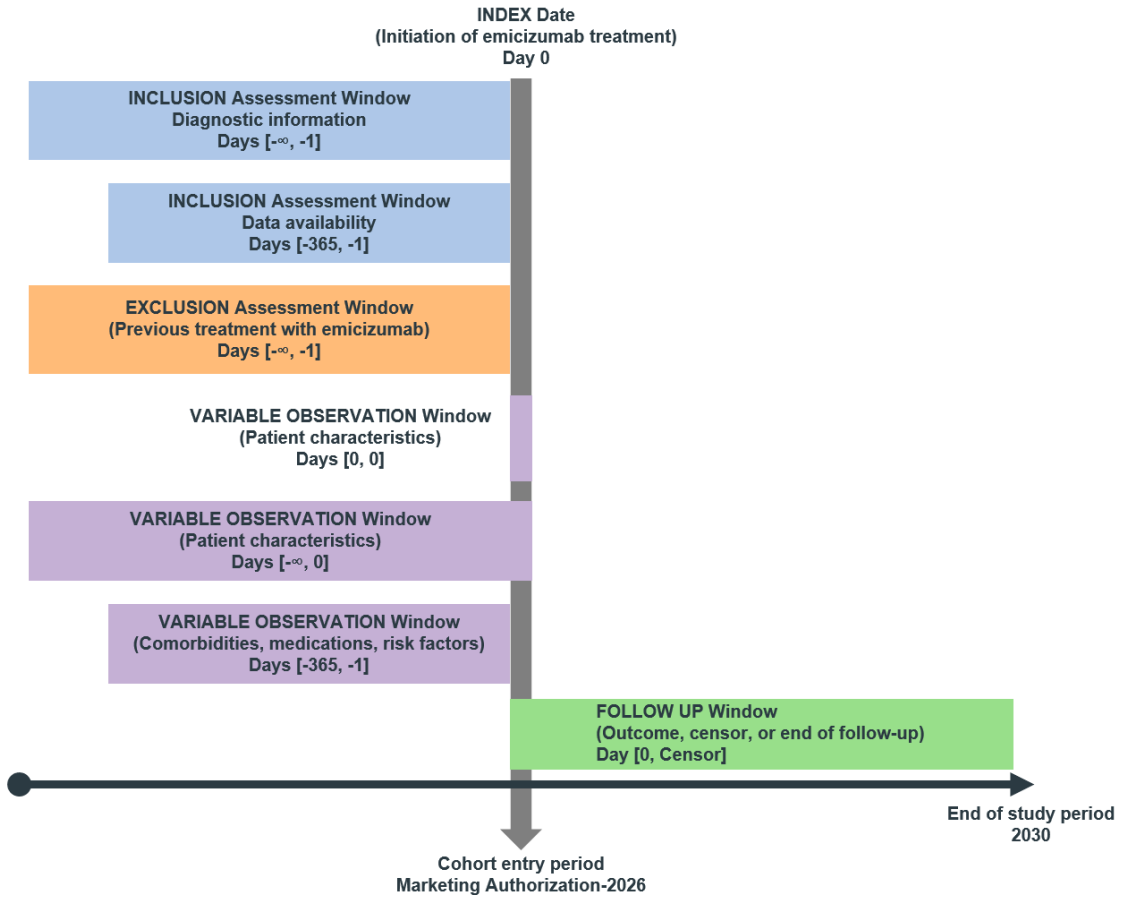

Figure 1. Overview of study design and assessment periods.

8.2. SETTING

The study will include patients with congenital HA who have moderate disease (1% ≤ FVIII ≤ 5%), without FVIII inhibitors and severe bleeding phenotype from registries in, but not limited to, the European region. This will provide a broad coverage of a large geographic area, covering different health care settings, and representing a diverse group of patients. Inclusion and exclusion criteria will be applied to select an eligible study population for this study, this will be as subset of the overall patient population in the considered data sources (see section 8.2.6).

The specific registries were determined in a feasibility assessment conducted between April 2023 and October 2023 to identify the most appropriate data sources for this study. A list of the registries that are considered for this study is given below. Actual participation is conditional to contracting.

- UK National Haemophilia Database (UKNHD)
- FranceCoag registry / Reseau FranceCoag

- HemoNED
- American Thrombosis and Hemostasis Network (ATHN dataset)
- World Bleeding Disorders Registry (WBDR)
- Canadian Bleeding Disorders Registry (CBDR)

Details on the registries considered for this study are provided in section 8.4.

8.2.1. Study Period

The study period will be defined as follows:

- **Start of study period** will be the defined as the date of MA of emicizumab for use among moderate patients without inhibitors in each participating country.
- **End of study period** will be the last date included in the data extraction across all participating countries (see section 5. For details), anticipated Q4 2030.

8.2.2. Cohort Entry Period

The cohort entry period, when the patients will be assessed in the data source for inclusion in the study, will last from MA of emicizumab for use among moderate patients without inhibitors in each participating country until approximately Q4 2026, to allow for a minimum of 4 year of follow-up until the end of the study period.

This will allow for patients using emicizumab to be included in locations where emicizumab has been approved earlier for use among HA patients with moderate severity, e.g., the US and Canada, before EMA protocol approval. In addition, protocol approval might have occurred after initiation of reimbursement discussion in several locations in Europe. Patients who initiated emicizumab before protocol approval will be considered for inclusion as long as re-consent is not required by the data sources, all other inclusion and exclusion criteria are fulfilled, and no major data enhancement is needed.

8.2.3. Index date

The index date will be the date of emicizumab treatment initiation for each patient during the cohort entry period.

8.2.4. Follow-up Period

The study will allow for a minimum of 4 years of follow-up after the index date. The follow-up period will be the time period from index date (first emicizumab initiation) until,

the end of the study period (anticipated Q4 2030), a maximum of 5 years of follow-up, or censoring.

8.2.5. Censoring

Patients will be followed until the end of study period or when meeting any of the following censoring criteria, the reason for censoring will be described, whichever occurs first:

- Death
- End of observation, e.g., due to loss to follow-up, emigration, or disenrollment from the registry
- Discontinuation of emicizumab treatment (as defined in the exposure section 8.3.2.2.)

8.2.6. Study Populations

HA patients that are naïve users of emicizumab will be selected based on the eligibility criteria presented below.

8.2.6.1. Inclusion Criteria

Patients must have met the following diagnostic criteria to be included in the study:

- Diagnosis of congenital HA.
- Moderate disease classification (1% ≤ FVIII ≤ 5%).
- Severe bleeding phenotype, defined as the patient previously having had spontaneous bleedings and for whom prophylaxis is required to prevent such bleeding or other life-threatening complications per physicians opinion or as otherwise noted in the data source (Srivastava et al., 2020). Severe bleeding phenotype will be captured using the following criteria:
    - Ongoing or previous prophylactic treatment with clotting FVIII infusions (Carcao et al., 2020) during the 12 months prior to the index date.

      Or:
    - Spontaneous bleeding, defined as a bleeding that was not caused by trauma or a medical procedure at any time in the past prior to the index date.

      Or:
    - An annualised bleeding rate (ABR) of ⩾2 events/year in the 12 months prior to the index date.

      Based on previous studies on bleeding phenotypes among moderate patients with haemophilia where ABR≥2 is above the 3rd ABR quartile (Kloosterman et al., 2022) or at the median and above (den Uijl et al., 2014).

  Due to the variability of reporting in the data sources, the exact operational definition of the severe bleeding phenotype will vary between data sources. Table 1 shows the different criteria that can be fulfilled in each specific database.

Table 1. Applicable criteria for severe bleeding phenotype in the considered data sources.

Data source	Country	Spontaneous bleeding prior to index date	Prophylactic treatment 12 months prior to index date	Annualised bleeding rate 12 months prior to index date
UKNHD	UK	Low	Low	Derived (number of new bleeding episodes at follow-up)
FranceCoag	France	Good	Good	Derived (bleeding events)
HemoNED	Netherlands	Captured	Captured	Derived (date/time of bleed, cause, location, and severity)
ATHN dataset	US	Not collected	Good*	Derived (bleed events)*
WBDR	Multi-country	Good	Good	Derived (total number of bleeds at baseline and at follow-up visits)
CBDR	Canada	Collected	Good	Derived (total number of bleeds)

*Bleed events not specified as traumatic or spontaneous.
UKNHD, UK National Haemophilia Database; **UK,** United Kingdom**; ATHNdataset**, American Thrombosis and Hemostasis Network; **US**; United States; **WBDR**, World Bleeding Disorders Registry; **CBDR**, Canadian Bleeding Disorders Registry.
Information from feasibility questionnaire or data dictionary: Good = >70% patients included in the disease registries have the required variable, Moderate = 40 – 70% patients with variable, Low <40% patients with variable, Captured = Not disclosed, Not collected = No patients with variable.

The above-mentioned inclusion criteria will ensure that the patient is eligible for the extended indication of emicizumab.

In addition, the patient will have to fulfil the following criteria:

- Initiation of emicizumab treatment during the cohort entry period.
- Information on previous HA outcomes and HA treatments approximately 12 months prior to the index date. In case HA diagnosis occurred within 12 months of the index date, the required lookback period will be shortened to time from HA diagnosis to index date. Anamnestic information capturing historic events but entered in the

registry database less than 12 months before the index date will be considered as long as they were recorded prior to the index date.

- Information on risk factors of TE events (e.g., medical comorbidities, treatments and demographic characteristics) approximately 12 months prior to the index date. If the patient is below 1 year of age, the lookback period will be shortened to birth until index date. Anamnestic information capturing historic events but entered in the registry database less than 12 months before the index date will be considered as long as they were recorded prior to the index date.
- Signed the informed consent form where required by local regulations.

8.2.6.2. Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Noted development of FVIII inhibitors in the data source any time before index date or fulfilling any of the following criteria of a previously developed algorithm (Batt et al., 2022):
  - Treatment with bypassing agents, such as aPCC or recombinant activated FVII (rFVIIa), at any time prior to the index date.
  - Treatment with rituximab at any time prior to the index date, this criterion would not apply if it was noted in the data source that it was used for another indication, e.g., treatment of lymphoma.
  - Noted use of assay to measure FVIII inhibitors (Duncan et al., 2013) and high dose of FVIII use at any time prior to the index date that is in line with immune tolerance induction. The exact definition of dosage in line with immune tolerance induction will be further defined in the statistical analysis plan (SAP) and may be data source specific.
- Treated with emicizumab at any time prior to the index date.

These criteria will ensure that the patient is eligible for the extended indication of emicizumab.

8.3. VARIABLES

A feasibility assessment was conducted between April 2023 and October 2023 to provide input on the availability of the variables in the data sources, the results from the feasibility are detailed in the respective sections. Given that availability of variables varies across registries some variable might require variable derivation. A detailed specification of the operationalisation of all variables will be given in the SAP. A summary of the variables of the study is given in Table 2.

Table 2. Summary list of variables.

Section	Variables	Described in section
Inclusion and exclusion criteria	• Diagnosis of congenital HA • FVIII level • FVIII inhibitor status • Severe bleeding phenotype • Initiation of emicizumab treatment • Previous treatment with emicizumab	8.2.6.1. 8.2.6.2.
Exposure	• Emicizumab treatment: o Start date o Stop date o Dose o Frequency o Reason for treatment o Length of treatment o Reason for discontinuation	8.3.2.2.
Censoring variables	• Date of death. • End of observation, e.g., due to loss to follow-up, emigration, or disenrollment from the registry. • Date of emicizumab treatment discontinuation.	8.2.5.
Safety variables	• SAEs o Number of events o Diagnosis o Start date o Outcome o Relatedness to treatment o Treatment of SAE • TE events o Number of events o Diagnosis o Start date o Outcome o Relatedness to treatment	8.3.1. 8.3.2.1.

Section	Variables	Described in section
	o Treatment of TE event • TMA o Number of events o Diagnosis o Start date o Outcome o Relatedness to treatment o Treatment of TMA event • Serious systemic hypersensitivity reactions, including anaphylaxis o Number of events o Diagnosis o Start date o Outcome o Relatedness to treatment o Treatment of serious systemic hypersensitivity reaction	
Patient's demographic characteristics	• Age • Sex • Ethnicity • Weight • Height • Country of residence	8.3.2.3.
Patient's haemophilia related characteristics	• Date of diagnosis of congenital HA • Any major complications: o Bleeding o Hemarthrosis o Infections from injections • Prior treatments for haemophilia	8.3.2.3.

Section	Variables	Described in section
Medical history	• Concomitant medications o Start date o End date • Other medical history and concurrent conditions	8.3.2.3.
Risk factors for TE events	• Known risk factors for TE events (see details below)	8.3.2.4.

HA, Haemophilia A**; TE,** Thromboembolic**; TMA,** Thrombotic Microangiopathy**; FVIII,** Coagulation Factor VIII**; SAE,** Serious Adverse Event**.**

8.3.1. Primary and Secondary Safety Variables

The primary safety variable is TE events as recorded in the data source.

The secondary safety variables are:

- TMA
- Serious systemic hypersensitivity reactions, including anaphylaxis
- SAEs (for definition of SAEs see section 10.1.2.)

The relationship to the treatment will be detailed according to available information in each registry. If this is not available in the registry, time to the first primary or secondary safety events will be described, for further details see section 8.7.

The reporting of AEs in the considered registers for further engagement differs, an overview is given in Table 3 and the details are provided below.

Table 3. Reporting of adverse events among the considered data sources.

Data source	Country	Coding standard
UKNHD	UK	Local adaptation of EUHASS
FranceCoag	France	EUHASS (ICD-10 used for further classification of malignant disorders)
HemoNED	Netherlands	EUHASS
ATHNdataset	US	SNOMED, MedDRA
WBDR	Multi-country	Standardised module
CBDR	Canada	CHESS

UKNHD, UK National haemophilia database; **UK,** United Kingdom**; EUHASS**, European Haemophilia Safety Surveillance; **ATHNdataset**, American Thrombosis and Hemostasis Network; **US**; United States; S**NOMED CT**, Systemized Nomenclature of Medicine – Clinical Terms**; MedDRA,** Medical Dictionary For Regulatory Activities**; WBDR**, World Bleeding Disorders Registry; **CBDR,** Canadian Bleeding Disorders Registry; **CHESS,** Canadian Hemophilia Surveillance System; **ICD,** International Classification Of Diseases.

The European Haemophila Safety Surveillance (EUHASS) system is a pharmacovigilance program that aims to monitor the safety of treatments for patients with haemophilia and other inherited bleeding disorders in Europe through a prospective AE reporting system. The program started in October 2008 and includes participating centres located across more than 30 European countries. The following events are reported to EUHASS either as they occur or as a minimum at the end of every 3-month surveillance period (European Haemophilia Safety Surveillance, n.d.):

- Acute or allergic events
- Transfusion-transmitted infections
- Inhibitors
- Thromboses
- Malignancies
- New cardiovascular events
- Neurological events
- Unexpected Poor Efficacy
- Other AE Possibly Related to Concentrate
- Deaths

For each event reported, data are collected on the patient's age, diagnosis and severity; as well as details about the product and batch numbers involved; and finally details about the event outcome and presence of other risk factors (Makris et al., 2011). Event-specific data are submitted anonymously using the Soundex coding system to avoid

duplicate reporting. EUHASS data are not collected according to the medical dictionary for regulatory activities (MedDRA) classifications; however, AEs have been previously aligned to MedDRA preferred terms.

For the UKNHD data source, event reporting has been harmonised with the EUHASS program, and any reported event from participating centres are anonymised and automatically forwarded to EUHASS by the National Haemophilia Database (NHD). Yet, whenever a new inhibitor is reported, the UK Haemophilia Centre Doctors' Organisation (UKHCDO) requests more detailed information, which is not passed onto EUHASS. The additional data requested by the UKHCDO when a new inhibitor is reported include (World Federation of Hemophilia, 2009):

- Coagulation disorder, severity, and genotype if known
- Any relatives with inhibitors
- First inhibitor detection date and the reason for the test
- Inhibitor value at first detection and maximum value
- Any change in the value of factor VIII- or factor IX-coagulant (FVIII:C or FIX:C)
- Any change in bleeding pattern
- Treatment protocol before inhibitor development
- Time in chronological and exposure days from first dose to inhibitor development

The Canadian Hemophilia Surveillance System (CHESS) uses the same methodology as the EUHASS program (Dolan et al., 2014).

For the WBDR data source, an AE module is available at both baseline (when the patient enrolled in the registry) and follow-up visits. When an AE is reported, the participant centre must complete the following fields:

- Start date of onset (i.e., the date the patient first experiences the AE)
- Events (Infection, allergic reaction including anaphylaxis, TE event, TMA, lack of efficacy, injection site reaction or other event)
- Date of resolution (i.e., the date by when the patient stops experiencing the AE)
- Interventions

8.3.2. Secondary Variables

8.3.2.1. Primary and Secondary Safety Variable Characteristics

Any primary or secondary safety variable event available in the data source will be further detailed regarding symptoms, diagnostic processes, and treatments. This includes but will not be limited to imaging, antithrombotic treatment, hospitalisation status and current additional treatments for haemophilia when available (see section

8.3.1. on the details provided in the respective data sources adverse event reporting system).

8.3.2.2. Exposure Definition

Exposure will be based on dates of prescriptions and dispenses, and details on the numbers of prescriptions and doses, as reported in the data source. The start of exposure (index date) is defined as the first prescription or injection of emicizumab, as noted in the data source. An overview of the variables available to define exposure during follow-up can be seen in Table 4. All registers cover the haemophilia related treatments: emicizumab, aPCC, Eptacog alfa (activated), and Factor VIII transfusions.

If the registry does not include information on exact stop dates of treatment exposure, as in the case of HemoNED, treatment will be considered ongoing for as long as new prescriptions, injections or dispenses are noted in the data source and are consistent with continuous treatment. To accommodate non-perfect adherence or other situations where the series of prescriptions are part of a continuous exposure period, an additional 90 days will be added to exposure period, at the last noted injection or at the end of prescribed supply, corresponding to 3 times the half-life of emicizumab when the patient will be considered no longer affected by the drug (Hallare and Gerriets, 2023). If the patient has not filled another prescription or received an injection at the end of the added 90 days, the exposure period will end. The definition of exposure might differ between data source and will be further defined in the SAP. Reason for treatment discontinuation will also be collected where available. Exposure of other treatments of interest, that were given prior to the index date, will be defined using a similar methodology that will be detailed in the SAP.

Table 4. Treatment information in each data source.

Register	Country	Start / stop dates	Dosage	Frequency	Reason for treatment*
UKNHD	UK	Captured	Captured	Captured	Captured
FranceCoag	France	Good	Good	Derived	Good
HemoNED	Netherlands	Moderate (start only)	Captured	Captured	Captured
ATHNdataset	US	Good	Good	Good	Good
WBDR	Multi-country	Good	Good	Good	Good
CBDR	Canada	Good	Good	Good	Good

Prophylaxis, on demand or other.
UKNHD, UK National Haemophilia Database; **UK,** United Kingdom**; ATHNdataset**, American Thrombosis and Hemostasis Network; **US**; United States; **WBDR**, World Bleeding Disorders Registry; **CBDR**, Canadian Bleeding Disorders Registry.
Information from feasibility questionnaire or data dictionary: Good = >70% patients included in the disease registries have the required variable, Moderate = 40 – 70% patients with variable, Low <40% patients with variable, Captured = Not disclosed, Derived = Derived from other variables in the dataset, Not collected = No patients with variable.

8.3.2.3. Patient Characteristics

The following patient characteristics will be collected from the data sources:

- Age
- Sex
- Ethnicity
- Weight
- Height
- Country of residence
- Date of diagnosis of congenital HA
- Any major complications (e.g., bleeding events, hemarthrosis, infections from injections)
- Prior treatments for haemophilia
- Concomitant medications
- Other medical history and concurrent conditions

The coverage of the different demographic and clinical characteristics in the considered registries shown are shown in Table 5 and Table 6.

Table 5. Demographic characteristics.

Data source name	Country	Age	Sex	Ethnicity	Weight and height
UKNHD	UK	Captured	Captured	Captured	Captured
FranceCoag	France	Good	Good	Good	Good
HemoNED	Netherlands	Captured	Captured	Captured	Captured
ATHNdataset	US	Good	Good	Good	Good
WBDR	Multi-country	Good	Captured	Not collected	Good
CBDR	Canada	Good	Good	Low	Good

UKNHD, UK National Haemophilia Database; **UK,** United Kingdom**; ATHNdataset**, American Thrombosis and Hemostasis Network; **US**; United States; **WBDR**, World Bleeding Disorders Registry; **CBDR**, Canadian Bleeding Disorders Registry.

Information from feasibility questionnaire or data dictionary: Good = >70% patients included in the disease registries have the required variable, Moderate = 40% – 70% patients with variable, Low <40% patients with variable, Captured = Not disclosed, Not collected = No patients with variable.

Table 6. Clinical characteristics.

Data source	HA diagnosis	HA disease severity	HA treatments*	HA medical history	FVIII inhibitors	Laboratory measures	Current comorbidities	Concomitant medications
UKNHD	Good	Good	Good	Captured	Captured	Moderate	Captured	Captured
FranceCoag	Good	Good	Good	Moderate	Captured	Not collected	Good	Low
HemoNED	Captured	Captured	Captured	Captured	Captured	Moderate	Pending	Pending
ATHNdataset	Good	Good	Good	Good	Captured	Moderate	Good	Good
WBDR	Good	Good	Good	Good	Captured	Moderate	Good	Good
CBDR	Good	Good	Good	Good	Captured	Low	Low	Not collected

**Treatment with emicizumab, Anti-inhibitor coagulant complex use, Eptacog alfa (activated), FVIII*.
HA, Haemophilia A; **FVIII,** Coagulation Factor VIII; **UKNHD**, UK National Haemophilia Database; **UK,** United Kingdom**; ATHNdataset**, American Thrombosis and Hemostasis Network; **WBDR**, World Bleeding Disorders Registry; **CBDR**, Canadian Bleeding Disorders Registry.
Information from feasibility questionnaire or data dictionary: Good = >70% patients included in the disease registries have the required variable, Moderate = 40 – 70% patients with variable, Low<40% patients with variable, Captured = Not disclosed, Not collected = No patients with variable, Pending = Information requested from data source, awaiting reply.

8.3.2.4. Risk Factor Variables for TE Events

The following candidate variables will be used to characterise the patients TE risk profile and are assessed within one year prior to the index date. The candidate risk factors were chosen based reference literature regarding their relationship with TE events (den Heijer et al., 1996; Goldhaber, 2010; Heit, 2015; Keramidas et al., 2021; Lowe, 2008; Pastori et al., 2023; Raj et al., 2022). As the feasibility assessment did not provide detailed information on the availability of all TE risk factors, a full evaluation of the availability of the risk factors in each data source will be provided in the SAP. Risk factors considered to be included:

Patient characteristics:

- Advanced age (age > 50 years)
- Smoking
- Body Mass Index (BMI) (BMI ≥ 30 kg/m^2 i.e., obesity)
- Sex

Patient medical history:

- Previous TE event
- Venous insufficiency
- Myocardial infarction
- Ischaemic heart disease
- Coronary artery disease
- Cerebrovascular disease
- Peripheral vascular disease
- Heart failure
- Hypertension
- Atherosclerosis
- Diabetes
- Medical device use
- Moderate or severe liver disease
- Recent hospitalisation/surgery
- Previous or ongoing cancer
- Chronic Inflammatory Lung Diseases (including Chronic obstructive pulmonary disease [COPD], asthma, tuberculosis)
- Obstructive sleep apnea

- Lower limb paralysis
- Hyperhomocysteinemia
- Chronic kidney disease Stage 3 and above
- Recent trauma/ fractures
- Hormone replacement therapy including oral contraceptives
- Pregnancy/puerperium
- Infectious diseases (including sepsis, pneumonia, Covid-19 infection and Human Immunodeficiency Virus infection)
- Inflammatory disorders (including systemic lupus erythematosus [SLE], inflammatory bowel disease and rheumatoid arthritis)

8.4. DATA SOURCES

The data for this study will be collected from existing registries that include haemophilia patients living in the European region and in other countries. A feasibility assessment was performed between April 2023 and October 2023, designed against the EMA guidelines and requirements for registry-based studies (European Medicines Agency, 2021), to inform the selection of the registries for further engagement with the following objectives:

- Provide a general overview of HA disease registries in countries of interest, including details of their objectives, number of contributing sites, and funding sources.
- Assess the potential patient counts of moderate HA patients enrolled in each registry.
- Assess the availability, quality, completeness, frequency, and timeliness of variables required to meet the study requirements.
- Establish operational aspects of data management, including processes for data capture and validation.
- Describe current methods for identification and reporting on AEs, including adverse drug reactions and whether the relatedness to the treatment is reported.
- Identify any potential limitations, confounding factors and biases in the registries, as well as measures taken for mitigation.
- Outline any considerations relating to ethics, data privacy, informed consents, information governance and contracting.

Description of each of the registers was developed based on information collected from data holders and through desktop research. The full list of registries assessed can be found in Appendix 1. After the feasibility assessment the following registries were considered (listed in Table 7), these registries include a total of 5307 moderate HA patients. Participation of each data source is conditional to contracting.

Table 7.Overview of the considered registries.

Data source name	Data Collection Period	HA Patient Count	Moderate HA Patient Count	Longitudinal Follow-up	Data lag	Access to Patient-Level Data
UKNHD	1968 – Present	8959	836	YES	Up to 3 months	YES
FranceCoag	2003 – Present	7600	940	YES	Not specified	YES
HemoNED	2015- Present	1431	230	YES	2-3 weeks	YES
ATHNdataset	2020 - Present	100	15	YES	2-6 months	YES
WBDR	2018 – Present	10071	2987	YES	6 months	NO
CBDR	2015 – Present	2799	299	YES	Immediately available	NO

HA, Haemophilia A; **UKNHD**, UK National haemophilia database; **ATHNdataset**, American Thrombosis and Hemostasis Network; **WBDR**, World Bleeding Disorders Registry; **CBDR**, Canadian Bleeding Disorders Registry.

UK National Haemophilia Database (UKNHD)

The UKHCDO manages the UKNHD, which was established in 1968. All UK haemophilia centres are required to report to NHD on all patients with bleeding disorders. (UKCHDO, 2023). As of June 2023, 8959 patients diagnosed with HA were included in the database, and of those, 836 have moderate HA. Besides patient numbers and diagnosis, the database includes details of the type and quantity of treatment used for therapy and the complications of treatment (as described in section 8.3.1.). More recently, the Haemtrack application has allowed patients to report, via mobile apps or computers, their individual treatments, the reasons for those treatments (which includes, among other information, new bleeds, follow-up bleeds and prescribed treatments) and more details about the bleed episodes. The information uploaded by patients can be checked by their own haemophilia centre and treatment can be adjusted according to this information (UK National Haemophilia Database, 2020).

FranceCoag Registry / Reseau FranceCoag

The FranceCoag Network was established in 1994 to capture data on a cohort of French patients suffering from inherited deficiencies of coagulation proteins including HA disorder, at first the registry only included severe patients this was expanded in 2003 to include all patients with inherited bleeding disorders. The Network is a public institution hosted by both the Direction Recherche Santé (DRS) and Assistance Publique Hôpitaux de Marseille (AP-HM) and aims at improving epidemiological knowledge about inherited bleeding disorders in France. Patient data are collected after each follow-up visit from contributing sites via an electronic Case Report Form (CRF) and validated at least twice a year. This includes variables on demographics, treatment, medications, disease severity and diagnosis. The Network also captures both AEs and SAEs including international classification of diseases, tenth revision (ICD-10) only for malignant diseases (Doncarli et al., 2019). As of June 2023, the Network reported capturing data on more than 7000 HA patients including approximately 900 moderate HA patients.

HemoNED

HemoNED collects longitudinal data on patients with haemophilia and associated disorders in the Netherlands and is managed by the HemoNED Foundation, an initiative of the Dutch Haemophilia Treaters Society (NVHB) and the Netherlands Haemophilia Patient Society (NVHP). It was established in 2015. Practitioners treating haemophilia patients are able to enter data of their patients into the registry. Patients can also directly contribute to the registry by providing their medications and bleedings status in a digital infusion log (app), which is accessible to both the practitioner and the patient. The registry reports side effects of medication to both the Netherlands Pharmacovigilance centre and the EUHASS database (HemoNED). As of June 2023, the registry captured data on more than 1400 HA patients out of which 230 had moderate disease. Among others, data on diagnosis, disease severity, treatments, medications, demographics and bleeding events are periodically collected in the registry.

American Thrombosis and Hemostasis Network (ATHN)

The ATHN is a natural history cohort collecting data from patients with congenital or acquired non-neoplastic haematologic disorders. Data collection started on 2020 and includes information on demographics, clinical patient characteristics, treatments, medications, disease severity, diagnosis, inhibitor status among others. The data arecollected via an electronic CRF both from patients in the US and Pakistan. AEs are collected using SNOMED, and MedDRA standards including capture of TMA and TE events (American Thrombosis & Hemostasis Network, 2023). As of June 2023, a total of 100 patients with HA were reported including 15 patients with moderate HA.

World Bleeding Disorders Registry (WBDR)

The WBDR is a web-based data entry system established in January 2018 by the World Federation of Hemophilia (WFH). It aims to provide a platform for a network of treatment

centres to collect uniform and standardised data on people with HA or B, or von Willebrand Disease. As of February 2022, 96 participating centres from 46 countries had access to the WBDR (World Bleeding Disorders Registry, 2020). As of June 2023, a total of 10071 HA patients were estimated in the database, including 2987 with moderate HA. Data collection occurs at the level of participating treatment centres and includes a minimal data set that provides basic information on demographics, diagnostics, inhibitor status, bleeding events, joint disease, treatment, hospitalisation and mortality; as well as an extended data set that provides expanded details on the variables covered in the minimal dataset (Barbara Konkle et al., 2020).

Canadian Bleeding Disorders Registry (CBDR)

The CBDR, launched in July 2015, is a clinical database that collects information on virtually all patients affected by bleeding disorders in Canada, using a standardised dataset, data quality control processes, and incentivising mechanisms for Canadian Hemophilia Treatment Centres. As of June 2023, a total of 2799 HA patients were in the database, which included 299 patients with moderate HA. CHESS is a haemophilia surveillance system that was introduced in 2015, capturing data related to treatment safety and efficacy, plasma clotting factor utilisation and HRQoL data; and is compatible with the other data collection resources operating in Canada (Canadian Health Registry/ Canadian Hemophilia Assessment and Resource Management information System). The CBDR database is owned by the Association of Hemophilia Clinic Directors of Canada, and McMaster University is the data custodian. Patient demographics, clinical data, treatment usage and outcome data are collected via two main mechanisms: patients can enter information about their treatment and the bleeding events into the myCBDR app; and clinicians and others involved in the care of the patient can add specific data as part of documenting clinical interactions with the patient (Iorio et al., 2022).

8.5. STUDY SIZE

The study aims to include all available patients exposed to emicizumab with moderate congenital HA without FVIII inhibitors and with severe bleeding phenotype. In section 8.5.1. a real-world estimate is presented of expected number of eligible patients who can be included within the study period, based on a feasibility assessment. To assess whether this expected number of eligible patients will be adequate to investigate the primary study objective of determining the crude incidence rate (IR) of 1st TE, a simulation based statistical estimation is presented in section 8.5.2.

8.5.1. Expected emicizumab uptake in the patient population

Using information from the feasibility assessment conducted between April and October 2023 and the assumptions listed below, 2 scenarios of expected number of emicizumab patients during the cohort entry period (MA- 2026) were made. One scenario including

all available data sources and one restricted to data within the EU as the extension of indication for emicizumab to include prophylaxis in patients with HA without FVIII inhibitors, moderate disease severity and severe bleeding phenotype occurred recently in the EU (23 January 2023).

- **Assumption 1:** Inhibitor prevalence of 10% for moderate HA patients (Witmer and Young, 2013).
- **Assumption 2:** Severe bleeding phenotype prevalence of 30% among moderate HA patients without inhibitors based on requiring some form of prophylaxis (den Uijl et al., 2014).
- **Assumption 3:** Registry-based numbers of moderate HA patients treated with emicizumab roughly correspond to those with inhibitors (*patients without inhibitors are expected to be captured at least 12 months after the label extension approval due to later reimbursement approvals and data lag in the registries*). In addition, due to the feasibility assessment including patients from registries based in the US and Canada and the earlier approval of an extension of indication among moderate HA patients without inhibitors in these countries, the validity of assumption 3 could be affected. To reduce the impact of this, a more conservative scenario where the calculation was only based on feasibility information originating from countries within the EU was also calculated. Finally, MA most often comes before reimbursement approval, however, this is true for both periods and it is assumed that it will not impact the overall estimation.
- **Assumption 4:** Moderate HA patient population without inhibitors uptake during the cohort entry period (MA [2023 in the EU] - 2026) is expected to be equal to moderate patient HA population with inhibitor uptake (MA [2018 in the EU] - feasibility assessment).

To derive the uptake percentage of emicizumab, the above assumptions were utilised in the data from the feasibility assessment as below to produce the following uptake scenarios. Scenario 1 included all available data sources and scenario 2 was restricted to data within the EU.

1. The feasibility assessment reported 54 patients treated with emicizumab among 1319 patients with moderate HA, 4 registries (ATHNdataset, CBDR, FranceCoag and CNHPR) provided data on the number of emicizumab users in their moderate patient population. Given that ~10% of the moderate HA patient population have inhibitors (assumption 1), ~132 patients out of the 1319 patients would be eligible for treatment with emicizumab, as the approved indication for emicizumab was only for moderate HA patients with inhibitors when these data were collected (assumption 3).This indicates that the uptake percentage is approximately 40% (54/132). The above calculation of 40% is also in line with internal Roche data on uptake among moderate HA patients with inhibitors of ~45% and only slightly lower than an earlier projected uptake of emicizumab for 2023 in severe patients without inhibitors (Stonebraker and Ducore, 2021).
2. In the second scenario only patients from data sources within the EU (FranceCoag and Czech National Haemophilia Programme [this registry is not

considered for inclusion in the study but contributed information on the number of moderate patients currently treated with emicizumab]) were included, increasing the validity of assumption 3, as treatment with emicizumab among moderate patients without inhibitors was approved in 2023. The feasibility assessment found 1005 moderate patients out of which 26 were treated with emicizumab. Applying the same assumptions as was made in the example above an expected uptake of 25% was derived.

Using the uptake percentages presented above, projections of the expected study size for patients in the extended indication until 2026 are provided. It is assumed that the uptake in patients without inhibitors will be similar to that of moderate patients with inhibitors (assumption 4). In addition, based on assumption 1, the study cohort consists of 90% of moderate HA patients without inhibitors. Out of those, 30 % will have a severe bleeding phenotype (assumption 2). Four study size scenarios are presented in Table 8.

Table 8. Emicizumab uptake among moderate HA patients without inhibitors and severe bleeding phenotype.

Scenarios explored	Total study population of moderate HA patients in registries	Expected HA patients without inhibitors (90%)	Expected moderate HA patients with severe bleeding phenotype (30%)	Uptake % of emicizumab	Expected moderate HA patients initiating emicizumab
Using all data sources for uptake %*	5000*	4500	1350	40%	540
	3000	2700	810	40%	324
Using EU only data sources for uptake %*	5000*	4500	1350	25%	338
	3000	2700	810	25%	202

*Approximate total expected moderate patient population in all considered registries.
HA, Haemophilia A; **EU**, European Union.

For the study cohort, using a conservative estimate with a total study population of 3000 moderate HA patients (as indicated in Table 8), we project ~202 patients newly exposed to emicizumab to be captured within the cohort entry period (MA- 2026).

8.5.2. Minimum required sample size

To assess whether the real-world estimate obtained in section 8.5.1. will be adequate to investigate the primary study objective of determining the crude IR of 1st TE, a statistical estimation is presented below. A target sample size of ~200 exposed patients with an average follow-up of 4 years for each patient was considered. From simulation runs, this target sample size will ensure 88% probability that the 95% Clopper-Pearson confidence

interval (CI) of the crude IR does not exceed a threshold value of one event per 100 person-years (PY), considering the expected IR of AEs for the primary objective of 0.15 events per 100 PY.

In the emicizumab clinical trial program, a 0.38% incidence risk (3 out of 798 patients) was observed and an IR of 0.15 events per 100 PY with a 95% CI (0.03-0.44) for serious TE events not associated with concomitant aPCC in HA patients. The average duration of exposure was 138 weeks (2.65 years), with a median duration of exposure of 104 weeks (2 years). These findings align with the TE event risk observed in the European Haemophilia Safety Surveillance (EUHASS) registry, which was 0.40% (4 out of 1319 patients).

Table 9 presents alternative scenarios for the estimation's accuracy, defined as the probability that the upper limit of the IR 95% CI does not exceed a certain threshold. This is obtained via calculations with different target sample sizes. For the first alternative scenario, the same expected event rate as above is assumed, and the threshold value for the 95% CI remains as indicated previously. In the second scenario the expected event rate is increased to 0.5 per 100 PY and the threshold value for the 95% CI is changed to 1.5 events per 100 PY.

Table 9. Accuracy estimation for different targets of sample sizes, expected event rates and Clopper-Pearson 95% CI threshold values.

Target Sample Size	Accuracy CI	
	Expected event rate: 0.15 per 100 PY Threshold: 1 event per 100 PY	**Expected event rate: 0.5 per 100 PY Threshold: 1.5 event per 100 PY**
N=175	72%	73%
N=200	88%	79%
N=225	95%	83%

CI, Confidence Interval; **N,** Sample Size; **PY,** Person Years.

8.6. DATA MANAGEMENT

IQVIA is anticipated to perform the data management and statistical analyses. IQVIA will conduct this PASS on behalf of the MAH and will be responsible for applying for the applicable study permits, obtaining necessary approvals (ethical or otherwise), and accessing the study data. The data will be stored and analysed in accordance with local policy based on the country in which each registry is based. The primary data holders collect and manage data according to their own standards.

It is anticipated that the data holders will make data accessible to IQVIA, according to data permits in each specific country. The details of the data permits will be confirmed only once the data permits are granted. If the data permits allow patient-level data (PLD) will be accessed by IQVIA, otherwise only aggregate data will be transferred to IQVIA. All PLD accessible to IQVIA will have original personal identifiers replaced with a study identification number. Thus, IQVIA will not have access to data that allow patients to be directly identified. Following the extraction from the data sources, anonymised data will be stored at secure IQVIA servers or at other secure location in accordance with requirements of the data sources. Access to the data will be restricted to relevant personnel. It is not anticipated for the MAH to have access to the PLD. If the IQVIA is not granted access to PLD aggregated will be accessed by IQVIA using a CDM, as described in more detail below.

IQVIA will adhere to all local and regional laws on data protection and privacy set forth by each of the study countries. IQVIA will also adhere to IQVIA standard operating procedures (SOPs); data management for this study will be conducted using standard IQVIA processes. IQVIA will maintain appropriate data storage, including periodic backup of files and archiving procedures and will comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans and performing quality checks for all programmes.

The general principles of data management and statistical analyses will be described in detail in the Data Management Plan (DMP) and SAP, respectively. Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control (QC) checks of all programmes. All data checks to be performed on completeness, plausibility, and consistency of collected data will be described in detail with identification of data discrepancies.

Data will be harmonised and standardised as appropriate using a CDM. Within each data source, a CDM will be used to create aggregated datasets from the collected PLD in a pre-defined standard format. This CDM defines appropriate level of aggregation and minimum information required to enable the statistical analysis of the study objectives.

For registries with only aggregated data transfer and no access to PLD by IQVIA, the CDM will be applied by the data provider to create the aggregated data from the specific data source based on data specifications provided by IQVIA. These aggregated datasets are then delivered to IQVIA who then will perform the centralised data collection and statistical analysis of the study. In such cases, only aggregated data will be transferred to IQVIA servers.

For an overview of the data sources that allow for access to PLD, please refer to Table 7.

Once at the IQVIA servers, the aggregated data originating from the data sources will be combined with the aggregated PLD analysed by IQVIA.

A brief overview of the proposed CDM workflow depicting the different stages as described above is shown in Figure 2. The workflow presented constitutes a high-level overview of the CDM process and exact details especially how this would translate to the underlying programming pipeline and output generation will be detailed in DMP and SAP.

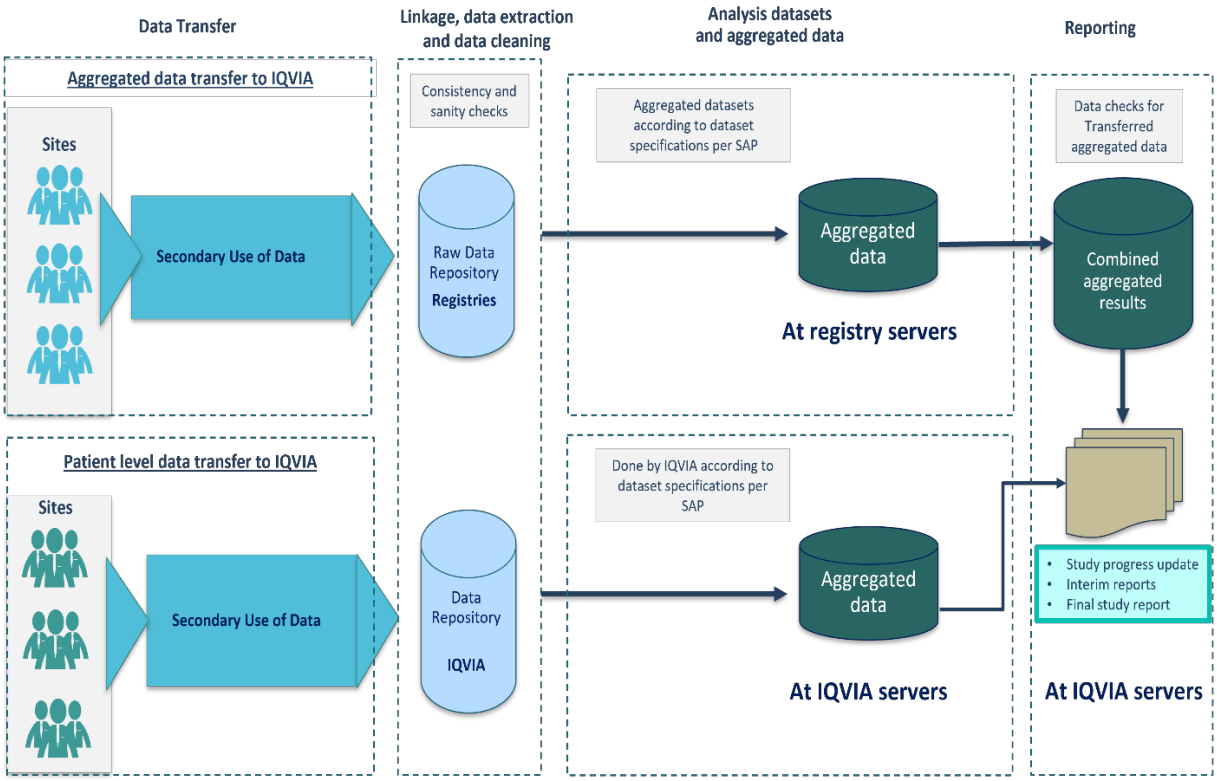

Figure 2. A high-level overview of CDM workflow.

IQVIA will develop a DMP for the purpose of this study. DMP will be created before data collection begins and will describe in detail all data checks to be performed on completeness, plausibility, and consistency for collected data and all steps necessary from raw data to final database such as, but not limited to, database development, additional data collection process, medical coding considerations and conventions, query edition and database validation.

8.7. DATA ANALYSIS

8.7.1. General Considerations

This study does not include any formal comparison and is purely descriptive. The following sections describe the analyses that will be carried out. Data analyses might be stratified as described in section 8.7.3. depending on data availability and final patient counts. In addition, no formal comparisons will be conducted between prophylaxis vs non-prophylaxis-treated patients (last previous treatment before the patient started emicizumab). Patient demographic and clinical characteristics will therefore be included in the descriptive analyses presented by patient subgroups. A full description of the analytical approach, data derivations, category definitions, analyses and presentation of the study results will be detailed in the SAP.

8.7.2. Planned Analyses

For the analysis of the primary objective and secondary objectives 1, 2, and 3 the overall crude and crude stratified IRs will be calculated. The person-time of each patient will be based on the follow-up and censoring criteria presented in section 8.2.4. and 8.2.5.

For the calculation of crude IRs, the denominator will be the pooled person-time of all the patients within the cohort. The patient time-at-risk will be calculated from index date until the date of an incident event or censoring, whichever occurs first. All first events occurring during follow-up period will be counted in the total number of events. Crude IRs will be presented per 100 PY with 95% CI.

For the primary objective, the numerator will be the number of first TE events of all patients within the cohort. For secondary objectives 1, 2, 3 the numerator will be the number of first occurrences of any SAE; TMA events or serious systemic hypersensitivity reactions, including anaphylaxis; respectively.

For the analysis of secondary objective 4, calculation of crude stratified IRs of 1st TE events will be done. The events will be counted for each category/stratum of relevant pre-defined risk factors (see section 8.3.2.4. for a listing of considered risk factors). More details on the risk factor based tabulations will be presented in SAP.

For analysis of secondary objective 5, characteristics of TE events, SAEs, TMA, and serious systemic hypersensitivity reactions, including anaphylaxis (e.g., diagnosis and symptoms), will be tabulated. In addition, time to 1st TE event; time to 1st TMA event; time to 1st serious systemic hypersensitivity reactions, including anaphylaxis; and time to any 1st SAE event will be described by Kaplan-Meier curves.

For analysis of secondary objective 6, calculation of crude IR and crude incidence proportion of TE, TMA events, SAEs and serious systemic hypersensitivity reactions,

including anaphylaxis, will be calculated and tabulated for FVIII prophylaxis use (yes/no) prior to emicizumab treatment.

Patient demographic and clinical characteristics will also be tabulated in relation to the AEs (TE events, SAEs, TMA events and serious systemic hypersensitivity reactions, including anaphylaxis) and in total.

Continuous variables will be described using mean, standard deviation, median, first and third quartiles, interquartile range, minimum and maximum, as appropriate. Categorical variables will be described by means of counts and percentages (relative to the number of non-missing observations for each variable).

8.7.3. Subgroup Analyses

Subgroup analyses will be carried out for all study objectives (section 7). Analyses specific to each group will be prioritised/de-prioritised following review of patient's numbers for each group. Subgroups of interest include, but are not limited to:

- FVIII prophylaxis use prior to emicizumab treatment initiation (yes/no) in line with secondary objective 6.
- Analysis by geographical regions (Europe; US and Canada; Other).
- Cardiovascular disease including treatment for cardiovascular disease, if feasible (yes/no) prior to emicizumab treatment initiation.
- Age at emicizumab treatment initiation (<50, ≥50 years-old).

All variables that are used to define subgroups will be assessed at the index date which is emicizumab treatment initiation. Further details on subgroups, their categories, and criteria for regrouping of any categories will be described in the SAP.

8.7.4. Sensitivity Analyses

The study will include 4 sensitivity analyses which will be performed on the study objectives. The sensitivity analyses are presented in Table 10 using the HARPER table template for sensitivity analyses (Wang et al., 2023).

Table 10. Sensitivity analyses – rationale, strengths and limitations.

Sensitivity analysis	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary analysis	Limitations of the sensitivity analysis compared to the primary analysis
1	Censoring not done at the end of treatment.	To determine the impact of possible information bias arising from informative censoring and the impact of long-term effects. The approach will be similar to an ITT analysis.	Long-term effects could be masked by censoring at end of treatment. Furthermore, treatment cessation could be linked to AEs.	The causal nature of the relationship between event and end of treatment will be difficult to evaluate if the event occurs long after the end of treatment.
2	All events, not just the first, will be counted for the rate and follow-up continues until end of study period	To determine the impact of all irrespective of 1st or subsequent outcomes during follow-up.	Full evaluation of the rate of AEs' burden across the follow-up.	All events during study period will measure the all-event rate, wherein all events (incident or subsequent) will be treated as independent. Events will be counted in the numerator for crude event rates and denominator will be the length of follow-up period until end of study period.
3	The maximum length of follow-up will not be set to five-years.	Further determine the long-term safety of emicizumab in the patient population.	Longer follow-up.	Longer follow-up will be correlated with geographical region, due to differences in time of MA, with a likely overrepresentation of patients with a follow-up longer than 5 years outside the EU.

Sensitivity analysis	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary analysis	Limitations of the sensitivity analysis compared to the primary analysis
4	Varying the definition of severe bleeding phenotype using two definitions based on criteria for which all ingoing registries have coverage of both criteria. These definitions will be applied and analysed in two separate sensitivity analyses: a. ABR>=2 in the 12 months prior to index date OR prophylactic treatment with clotting FVIII infusions 12 months prior to the index date b. Spontaneous bleeding at any time prior to the index date OR prophylactic treatment with clotting FVIII infusions 12 months prior to the index date	All data sources do not collect all criteria for severe bleeding phenotype (see Table 6). This can result in selection bias wherein patients are included based on the availability of the differing criteria across data sources. By varying the criteria of the severe bleeding phenotype definition in two sensitivity analyses we will test its robustness and gauge potential selection bias.	This will create similar selection criteria across all registries thus reducing potential differential selection across registries.	All three criteria of severe bleeding phenotype are important thus limiting the definition of severe bleeding phenotype might coincidentally introduce other forms of selection bias. As ABR might require both baseline and follow-up visits in the registry, this could result in a smaller sample size in some data sources. Not all registries will be able to fulfil both criteria (see Table 1 for details).

ABR, Annual Bleeding Rate; **AEs**, Adverse Events; **EU**, European Union; **ITT**, Intention to treat; **MA**, Market Authorisation.

8.7.5. Handling of Missing Data

For the current study, the feasibility assessment has clarified the level of reporting of key study variables (see Table 1, Table 4, Table 5 and Table 6). Methods commonly used in NI studies for handling missing data will be applied. The number of patients with missing data will be reported for each measured variable in the study. For the descriptive tables, missing data will be described separately and not included in the denominator for the calculation of the percentage for each category of a particular variable. Full details on handling of missing data will be described in detail in the SAP.

8.8. DATA QUALITY ASSURANCE AND QUALITY CONTROL

IQVIA will maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of Institutional Review Board/ Independent Ethics Committee (IRB/IEC) and governmental approval or notification (if required).

IQVIA shall ensure that the datasets and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Retention of Records

Archiving at the study site has to be for at least 5 years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by MAH for at least 5 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the MAH. Written notification should be provided to the MAH prior to transferring any records to another party or moving them to another location.

Quality Control

The study will be conducted according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the International Society for Pharmacoepidemiology, Good Pharmacoepidemiology Practice (GPP) Guidelines and IQVIA SOPs. At the study level, all aspects of the study from protocol development to the reporting of the results are conducted within the work frame

of IQVIA Quality Management System and in accordance with the appropriate global procedure.

According to the above-mentioned policies and procedures, Standard procedures will be used to ensure data quality and integrity, including quality checks described in section 8.6. and a QC checklist is developed and executed for the study, which includes QC on study methodology, SAP, programming, data management and analysis, study results, conclusions and study report. Furthermore:

- The study QC plan establishes ownership for the execution of the individual QC steps. The principle of the independence of QC applies.
- Individuals responsible for the execution of specific QC steps must have knowledge, capability and experience which are adequate for the task.
- The result of the execution of the individual steps of the QC plan is documented, and includes the required corrective actions, if any.
- The execution of any required corrective action is documented.

The executed QC plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.

The Investigator will comply with the confidentiality policy as described in the site contract, with the requirements described in the protocol. The treating physician is ultimately responsible for the conduct of all aspects of the PASS at the local level and verifies the integrity of all data transmitted to the IQVIA.

In compliance with regulatory requirements, the MAH, a third party on behalf of the Sponsor, or regulatory agencies may conduct quality assurance audits/inspections at any time during or following the study. The investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors/inspectors in order to discuss findings and issues. The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual study report, will be subject to independent Clinical Quality Assurance.

8.9. LIMITATIONS OF THE RESEARCH METHOD

8.9.1. Selection Bias

There is a possibility of selection bias if the registries to be included cover a select subset of patients that do not represent the overall patient population. However, the selected patient population is in need of specialised haematological care and the likelihood that any of the patient would be treated only in primary care is low as HA patients require specialised care. Another potential source of selection bias is that clinics

that are part of networks that report to specialised haemophilia registries might deliver higher quality of care resulting in a better safety profile. Nonetheless, the wide preliminary selection of registries with different coverage and geographical locations should help counter this selection bias.

It is likely that even within the patient group in the study at hand, i.e., patients with congenital HA without FVIII inhibitors who have moderate disease (1% ≤ FVIII ≤ 5%) and severe bleeding phenotype, there will be differences between those who receive emicizumab, compared with those who do not. That is, it is likely that the patients receiving emicizumab would be on the lower end of the FVIII interval closer to 1% with a higher risk of bleeding (Tiede et al., 2021). A thorough patient evaluation will be conducted to investigate the patients included in the study and report these descriptive statistics based on the patient's medical history.

The inclusion criterium for severe bleeding phenotype is based fulfilling either one of three criteria that are based on information regarding previous prophylactic treatment with FVIII infusions, previous spontaneous bleeding events and ABR. All data sources do not collect information regarding all of these criteria and the data sources might have different levels of completeness in the variables underlying the criteria. This can result in selection bias wherein patients in some registries are included based on the availability of the different criteria. To test the robustness of the severe bleeding phenotype definition and the variability in the outcomes that results from this, we will perform 2 sensitivity analyses where the severe bleeding phenotype criteria are varied.

8.9.2. Information Bias

Information bias is the bias arising from the systematic measurement error or misclassification of patients. As this is a registry-based study the validity of the findings of the study will solely rely on the validity, quality and completeness of the information recorded in the registries. There is potential for heterogeneity in the type of data collected from the registries regarding emicizumab treatment exposure, e.g., the exact dates of dispenses and SC injections, that could potentially result in exposure misclassification that are registry specific. Depending on the registry, specific limitations for exposure classification could be developed to avoid misclassification. There is also potential for heterogeneity in the study population because of different lookback periods when patients enrol in different registries. In certain cases, the lookback period might not be fully 12 months and the inclusion criteria regarding previous HA outcomes and HA treatments approximately 12 months prior to the index date (see section 8.2.6.1.) may not be fully confirmed if emicizumab treatment initiation (index date) coincides with patient enrolment into the registry.

In the primary incidence analysis, we do not exclude patients with a history of TE events before the index date. Thus, there exists a possibility that individuals with prior TE

events are included in the crude IR of TE. In the planned analysis of secondary objective 4 the IR would be tabulated based on the history of TE events during the lookback period. This would ensure that the incidence would be calculated for patients treated with emicizumab without any prior TE events during the lookback period and in addition contribute valuable evidence on the event rate among patients treated with emicizumab who have a history of TE events.

When calculating the crude IRs for our safety events of interest, the MAH will also test the possibility of information bias caused by the long-term effects of the treatment and informative censoring. For this, a sensitivity analysis will be performed using an ITT analysis where all patients initiating treatment with emicizumab will be followed until the end of the study period without censoring at emicizumab treatment discontinuation. This is to consider the potential impact of long-term treatment effects even after cessation of the treatment and assess the impact of informative censoring due to patients ending treatment early because of subclinical signs of an AE.

9. PROTECTION OF HUMAN PATIENTS

9.1. INFORMED CONSENT

The MAH will identify whether a new informed consent form is needed for using the data from the registries. For example, in some cases, additional patient informed consent forms or information letters indicating that the data will be transferred to another organisation for analysis may be required and will have to be obtained from individual patients depending on the rules and regulations setup by the data source or local authorities.

In addition to ensuring whether informed consent is needed certain precautions will be taken, including:

- Ensuring data are anonymised / pseudonymised
- Ensuring final analysis data are anonymised / pseudonymised
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled
- Obtaining ethical committee approval for use of data as proposed (e.g., the review of and extraction of information from individual medical charts) records for the proposed use ahead of study initiation

9.2. CONFIDENTIALITY

It is not anticipated for the MAH to have access to PLD. Following the extraction from the data source, anonymised data will be stored at secure IQVIA servers or at other secure location in accordance with requirements of the data source. Access to the data will be

restricted to relevant personnel. This means that patient names are not included in datasets that are transmitted to any MAH location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorisation for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Every effort will be made to protect participant confidentiality in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation).

9.3. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the GPP guidelines published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted. The study will comply with national and EU requirements for ensuring the well-being and rights of participants in NI post-authorisation safety studies.

9.4. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol and relevant supporting information must be submitted to the IRB/IEC, and reviewed and approved by the IRB/IEC before the study is initiated.

The MAH is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS(AES)

This is a NI PASS involving the use of secondary data and the reporting of adverse reactions in the form of Individual Case Safety Reports is not required.

The registries might however not collect AEs according to MedDRA Classification but by other coding systems, e.g., local adaptations of ICD-10, or in free text form. Whenever possible, the events will be mapped to common, pre-defined and approved study variables that will be detailed in the SAP.

All TE events and SAEs extracted from the data source for the study as specified in the protocol will be summarised as part of any interim safety analyses and in the final study report and final publication.

10.1. DEFINITIONS

10.1.1. Adverse Events (AEs)

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition);
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline (at the index date in the present study);
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.1.2. Serious Adverse Events (SAEs)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalisation
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician’s judgement (e.g., may jeopardise the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of NI PASS, the MAH is dedicated to openly providing information on the NI PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

In accordance with the 2010 EU pharmacovigilance legislation, information about this PASS will be entered into the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments and the final study report will also be entered in the register as appropriate. Interim reports will be included in the PSUR/PBRER.

The results of this study may be published or presented at scientific meetings. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements.

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ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: LONG-TERM NON-INTERVENTIONAL SAFETY STUDY OF EMICIZUMAB TREATMENT IN PATIENTS WITH MODERATE HAEMOPHILIA A AND SEVERE BLEEDING PHENOTYPE

EU PAS Register® number: To be added after registration.
Study reference number (if applicable): BO44691

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5.
1.1.2 End of data collection[2]	☒	☐	☐	5.
1.1.3 Progress report(s)	☐	☒	☐	5.
1.1.4 Interim report(s)	☒	☐	☐	5.
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5.
1.1.6 Final report of study results	☒	☐	☐	5.

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7.
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.
	2.1.2 The objective(s) of the study?	☒	☐	☐	7.
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1.
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2.
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.7.
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	8.3.1, 10.

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☐	☒	☐	8.1. , 8.2.
4.2	Is the planned study population defined in terms of:				8.1. , 8.2.
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2.6.

Comments:

Study has no age restrictions.

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.2.2.
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	8.3.2.2.
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.3.2.2.
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.3.2.2.
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.1
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	8.9.1.
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.2.

Comments:

Section 8: Effect measure modification		Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	8.7.3

Comments:

Section 9: Data sources		Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.3.2.2.
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.3.1.
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.3.2.3.
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.2.2.
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.1.
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.2.3.
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.2.2.
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3.1.
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

The study will be based on secondary data from existing HA disease registers including but not limited to those in the EU and US. HA disease registries that have been contacted and are under consideration in this study are listed in section 8.5.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5.
10.3 Are descriptive analyses included?	☒	☐	☐	8.7.
10.4 Are stratified analyses included?	☒	☐	☐	8.7.3
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.7.4
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.5.
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7.4

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6.
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.7.4. 8.9.
12.1.2 Information bias?	☒	☐	☐	8.7.4. , 8.9.
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.5.

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4.

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11.
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11.

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year

Signature: _____

13. APPENDIX 1

All disease registries evaluated during the feasibility assessment are listed in Table 11, below. Out of a total of 22 registries that were included in the outreach, IQVIA has shortlisted and prioritised a total of 8data sources considered for inclusion in the PASS. Sources were prioritised based on variable coverage, patient numbers, possibility of sharing PLD and responsiveness/willingness to engage. SAEs and AEs coverage was considered as a key element for inclusion in the list of prioritised sources. Registries that did not include coverage of SAEs/AEs were deemed not suitable and therefore ruled out. Further criteria for exclusion or deprioritisation of registries include lack of responses, unreliable engagement and self-reported failure to include emicizumab-treated patients.

Table 11. Full list of registries evaluated during feasibility assessment.

Disease Registry name	Geographical coverage	Disease Registry type	Number of total HA patients	Data collection start	Suitability assessment
UK National Haemophilia Database	National	Registry	8959	1968	Considered data source
FranceCoag registry	National	Registry	7600	2003	Considered data source
HemoNED	N/A	Registry	1431	2015	Considered data source
American Thrombosis and Haemostasis Network dataset	National	Registry	100	2020	Considered data source
World Bleeding Disorders Registry	International	Registry	10071	2018	Considered data source
Canadian Bleeding Disorders Registry	National	Registry	2799	2015	Considered data source
Czech National Haemophilia Programme	National	Registry	708	2011	Not suitable (Unstructured AE collection for outcomes of interest)
Clalit haemophilia registry	National	Registry data extracted from EMRs	800	2000	Not suitable (EMR data, unstructured AE collection)

Disease Registry name	Geographical coverage	Disease Registry type	Number of total HA patients	Data collection start	Suitability assessment
Australian Bleeding Disorders Registry	National	Registry	Unknown	1995	Information unavailable (Slow responses)
The Austrian Haemophilia Registry	National	Registry	Unknown	2009	Not suitable (No emicizumab patients)
Belgian Patient Haemophilia Association	N/A	Registry	Unknown	N/A	Not suitable (Limited or no AE collection)
Danish National Patient Register	National	Registry	354	1977	Not suitable (Limited or no AE collection)
The German Haemophilia Registry	National	Registry	4518	2008	Not suitable (Limited or no AE collection)
Irish National Haemophilia Register	N/A	Registry	Unknown	N/A	Information unavailable (Lack of responses)
Italian National Registry of Congenital Coagulopathies	National	Registry	Unknown	2005	Not suitable (Limited or no AE collection)
The International Registry RBD database	International	Registry	Unknown	2018	Information unavailable (Lack of responses)
Dutch National Haemophilia Complication Registry (KWARK)	National	Registry	Unknown	1992	Information unavailable (Lack of responses)
Portuguese National Registry for Haemophilia	N/A	Registry	Unknown	N/A	Information unavailable (Lack of engagement)
Spanish National Registry of Congenital Haemostatic Disorders	National	Registry	Unknown	N/A	Not suitable (No established network)

Disease Registry name	Geographical coverage	Disease Registry type	Number of total HA patients	Data collection start	Suitability assessment
Swedish National Registry for Bleedings Disorders	N/A	Registry	Unknown	N/A	Information unavailable (Lack of responses)
Swiss Haemophilia Registry	N/A	Registry	519	N/A	Not suitable (Limited or no AE collection)
Norwegian Centre for Rare Disorders	National	Registry	Unknown	1986	Information unavailable

AE, Adverse Event**; HA,** Haemophilia A. **N/A**, Non-applicable.