NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**EMICIZUMAB USE IN PEDIATRIC PATIENTS IN THE REAL WORLD: AN ANALYSIS OF THE PEDNET REGISTRY**
PROTOCOL NUMBER:	MO40685
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	EUPAS31954
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
AUTHOR:	[redacted], MD PhD, Principal Data Scientist, PHC Real World Data Oncology 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
03-Dec-2019 08:28:17	Deputy EU QPPV	[redacted]

ACTIVE SUBSTANCE:	Emicizumab
PRODUCT REFERENCE NUMBER:	NA
PROCEDURE NUMBER{S}:	EMEA/H/C/004406
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The main aim of this study is to assess safety of emicizumab use in children with hemophilia A in real world conditions, among pediatric patients enrolled in the PedNet Registry. The primary objective for this study is as follows: • To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and status of inhibitor Primary safety endpoints: Frequency and incidence of thromboembolic events (TE), thrombotic microangiopathy (TMA), and anaphylaxis The secondary objectives for this study are as follows: • To evaluate frequency and incidence of any adverse events reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor Secondary safety endpoints: Any AEs reported to PedNet Registry • To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor Secondary efficacy endpoints: Annual bleeding rate (ABR) for treated* bleeds and percentage of patients with zero treated bleeds ABR for joint bleeds, soft tissue bleeds, major bleeds, minor bleeds, and *As per PedNET data collection, all bleeds

	reported are treated bleeds
COUNTRIES OF STUDY POPULATION:	Countries with hemophilia centers participating in the PEDNET registry: Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Norway, Portugal, Spain, Sweden, Switzerland, The Netherlands, and United Kingdom
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	annual bleeding rate
AE	adverse event
BPA	bypassing agents
eCRF	electronic case report form
FVIII	blood coagulation factor VIII
HTC	Hemophilia Treatment Center
MAH	Marketing Authorization Holder
NI	non-interventional
PASS	Post-Authorization Safety Study
PedNet	European Pediatric Network for Haemophilia Management
PRAC	Pharmacovigilance Risk Assessment Committee
PT	preferred term
Q1W	once a week
SAE	serious adverse event
TE	thromboembolic event
TMA	thrombotic microangiopathy

2. RESPONSIBLE PARTIES

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Complementary information is given in Appendix 1

3. ABSTRACT/SYNOPSIS

TITLE:	**EMICIZUMAB USE IN PEDIATRIC PATIENTS IN THE REAL WORLD: AN ANALYSIS OF THE PEDNET REGISTRY**
PROTOCOL NUMBER:	MO40685
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	19 October 2018
EU PAS REGISTER NUMBER:	EUPAS31954
STUDIED MEDICINAL PRODUCT:	Emicizumab, Hemlibra®
SCIENTIFIC RESPONSIBLE	[redacted], Genentech
MAIN AUTHOR:	[redacted], F.Hoffmann-La Roche AG
PHASE:	IV, non-interventional study
INDICATION:	Hemophilia A
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

Rationale and Background

Hemophilia A is an X-linked recessive bleeding disorder characterized by deficiency or absence of blood coagulation factor VIII (FVIII), which leads to a lifelong bleeding tendency. It is estimated that hemophilia occurs in approximately 1:5000 newborn males. Approximately 65% of people with hemophilia A have moderate or severe forms characterized by FVIII activity levels 1%–5% or <1%, respectively, leading to frequent spontaneous bleeding events with complications, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, and death.

Primary prophylaxis with FVIII replacement therapy, consisting of intravenous infusion of FVIII 2–4 times each week starting before or after the first bleed, has proven to minimize bleeding events and complications and has become standard-of-care among pediatric patients. Although effective when optimally administered, prophylaxis with intravenous infusion can be accompanied by significant burden of treatment with impact on the quality of life of both patients and their caregivers. Although patients on FVIII prophylaxis experience low numbers of bleeds, magnetic resonance imaging scans demonstrate progressive arthropathy in up to two-thirds of patients who receive a primary prophylaxis regimen, likely due to challenging adherence and subclinical bleeds associated with low FVIII trough levels.

The development of neutralizing antibodies (inhibitors) against FVIII occurs in up to 30% of patients after exposure to therapeutic FVIII concentrates and represents the most common complication of these therapies. Permanent eradication of inhibitors can be achieved in 60%–80% of patients by immune tolerance induction using intensive FVIII administration. In patients with high-titer inhibitors following re-challenge with FVIII, use of bypassing agents (BPAs) is required for the treatment and/or control of bleeding events. Unfortunately, the

hemostatic effect of bypassing agents is suboptimal, and these agents are associated with higher rate of adverse events (AEs) and treatment burden compared with those of FVIII concentrates in patients without inhibitors, in both children and adults.

Emicizumab (also known as Hemlibra®) is a humanized monoclonal modified immunoglobulin G4 antibody with a bispecific antibody structure. Given that emicizumab has no structural relationship to FVIII, its efficacy is not affected by the presence of FVIII inhibitors and is not expected to induce or enhance the development of inhibitors to FVIII or to other coagulation factors. Emicizumab has been evaluated in many clinical trials and approved by multiple countries.

While the results observed in the clinical trials supporting the benefit-risk assessment at the time of the marketing authorization application are compelling and demonstrate a favorable benefit-risk profile, experience with emicizumab in the pediatric population has been primarily based on pediatric patients with inhibitors. In addition, there is no clinical experience with emicizumab use in newborns (birth to Day 28 of life), who are vulnerable to development of severe bleeds.The post-approval evaluation of the drug's outcomes and utilization is vital to assessing whether the efficacy and safety profile observed in clinical trials match the real-world experience in all age groups. To address this, data collected by the European Pediatric Network for Haemophilia Management (PedNet) Registry will be extracted and analyzed according to the current protocol, and Annual Reports will be generated.

Research Question and Objectives

The main aim of this study is to assess safety of emicizumab in real world conditions, among pediatric patients enrolled in the PedNet Registry.

The primary objective for this study is as follows:

- To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and status of inhibitor
- Primary safety endpoints:

  Frequency and incidence of TEs, TMA, anaphylaxis

The secondary objectives for this study are as follows:

- To evaluate frequency and incidence of any adverse events reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor
- Secondary safety endpoints:

  Any AEs reported to PedNet Registry
- To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor

  Secondary effectiveness endpoints:

  ABR for treated* bleeds and percentage of patients with zero treated bleeds

  ABR for joint bleeds, ABR for soft tissue bleeds, ABR for major bleeds, ABR for minor bleeds.

  * As per PedNET data collection, all bleeds reported are treated bleeds

Study Design

This is a non-interventional, secondary data use Post-Authorization Safety Study relying on data collected as part of the PedNet Registry.

PedNet is a multicenter, observational research database that includes patients with FVIII/IX levels ≤0.025 IU/mL born after 1 January 2000 and treated in one of the participating Hemophilia Treatment Centers (HTCs). Currently 31 centers from 18 countries are participating in the Registry. The goal of the registry is to include full cohorts of all consecutive patients diagnosed and treated in each center of which information on treatment and outcomes (e.g., inhibitor development, bleeds) is collected from the time of hemophilia diagnosis or time of first treatment. To prevent selection bias, patients referred to a center after development of inhibitors will not be included in the database.

Data included in the registry will be collected using electronic case report forms. Baseline data that pertains to mode of delivery, neonatal events, diagnostic symptoms, FVIII/IX gene mutation, and family history of hemophilia and inhibitors will also be collected. All centers will collect detailed data on treatment and outcomes (including inhibitor development and bleeds) of patients with hemophilia during the first 50 days of exposure to coagulation factor concentrate products. Following this, the centers will continue to collect information at least annually until the patient reaches the age of 18. Additional information will be collected regarding surgeries, hospitalizations, and AEs.

A similar level of detail will be collected for patients treated with emicizumab prophylaxis. When patients treated with emicizumab receive coagulation factor concentrate products, type of product will be recorded. It is therefore possible to evaluate the relationship between the use of FVIII/BPAs and development of TE/TMA events for patients treated with emicizumab prophylaxis.

PedNet performs annual data extractions in January of each year. Following each data extraction, PedNet group will analyze the data according to this protocol and provide the MAH with Annual Emicizumab-Specific Reports.

Data Sources

PedNet is a collaboration of 31 pediatric HTCs in 18 countries (EU and Canada), providing an infrastructure for clinical research and management of children with hemophilia. The PedNet Registry started in 2003 and collects real-life data from all newly diagnosed children born with hemophilia and treated at the participating centers.

Data are collected through well-defined web-based Case Report Forms using a secure data-entry system capturing all aspects of hemophilia from birth to adolescence and adulthood. The database is hosted at [redacted] in the Netherlands. Centers are visited regularly for on-site data monitoring with frequency according to their size with audit of baseline information (all data entered) and bleed and medication information (10%–50% of the data entered). Data on inhibitor results are all checked and interpreted centrally. In addition to monitoring of source data, numerous pre-specified logical checks are performed on the dataset. All inconsistencies or suspected errors are resolved by queries to the centers. All centers have obtained approval of their local ethical committee according to local regulations. Prior to inclusion into the registry signed informed consent is obtained from the parents. If required by local regulations, additional consent is obtained from patients after reaching 12 years of age included in the registry.

Population

The following criteria describe the population eligible for this study, which will be a subset of the overall population participating in the PedNet Registry.

Inclusion criteria for inclusion in the PedNet registry:

- Diagnosis of hemophilia A
- Factor VIII activity <25%
- Treated in one of the participating centers

Additional inclusion for emicizumab-specific analysis:

- Received prophylactic treatment with emicizumab

Exclusion criteria for the PedNet registry:

- Referral to a participating HTC after development of inhibitors
- Informed consent for participation in the PedNet registry not obtained

Exclusion criteria for emicizumab-specific analysis:

- Inherited or acquired bleeding disorder other than hemophilia A

Variables

Primary Safety Variables

The primary variables for this study are as follows:

- TE, TMA events, anaphylaxis (including terms of systemic hypersensitivity, anaphylaxis, and anaphylactoid events)

Secondary Variables

The secondary variables for this study are as follows:

- Other AEs reported to the registry including new inhibitor development, unexpected poor efficacy, etc. Unexpected poor efficacy is included in "Other" category of AE collection in the PedNet registry eCRF.
- Bleeding event (yes/no)
- Bleed location (joint bleed, soft tissue bleed), severity (major versus minor*)

Note: Per PedNet protocol definition:

Major bleed: bleed characterized by pain, swelling, limitation of motion and failure to respond within 24 hours of treatment

Minor bleed: bleed characterized by minor pain, minimal swelling, minimal restriction of motion, resolving within 24 hours of treatment

Joint bleed: any complaint requiring treatment located in a joint

Soft tissue bleed: any complaint requiring treatment located outside the joints

- Concomitant administration of coagulation factor concentrate products (type and dose of product (FVIII product, aPCC, rFVIIa) and dose of these products) in patients receiving emicizumab.

The baseline variables for this study are as follows: Baseline is defined as at the time of starting emicizumab.

- Diagnosis of hemophilia A
- Exposure to emicizumab
- Age
- FVIII Inhibitor status

Study Size

The sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the PedNet Registry. As of January 2019, PedNet enrolled 1824 patients with hemophilia A, of which 1083 patients had severe disease and 203 patients had moderate disease. Of the patients with severe disease, 351 patients had inhibitor diagnosed between 2000 and 2019.

Assuming a constant sample size of patients with severe disease in the registry (N=1083 with severe disease, N=351 with inhibitor), and assuming that at least 15% of these patients will receive emicizumab during the 3 years of the study, the anticipated minimum sample size is expected to be n=162 for patients with severe disease and n=53 for patients with inhibitor at the end of this 3-year study. The table below presents possible sample sizes with the average adoption of the drug among these patients varies between 15%–75% during the study. The MAH acknowledges that these estimates may change if the total number of patients enrolled in the registry changes significantly during the study time.

Table 1 Possible Sample Sizes

Emicizumab Adoption	15%	25%	50%	75%
Number of patients without inhibitor and with severe disease treated with emicizumab [a]	162	271	542	812
Number of patients with inhibitor treated with emicizumab [a]	53	88	176	263

a based on N=1083 patients with severe disease and N=351 with inhibitor enrolled in the PedNet registry as of January 2019

Data Analysis

General principles for data analysis are provided below.

Safety analyses will include the combined and separated population of patients with and without inhibitors, using all authorized emicizumab dosing regimens. Proportions of patients developing each type of AE (e.g., TE, TMA, and anaphylaxis) will be calculated along with the corresponding 95% CIs, and will be reported for all patients as well as in age-defined subgroups including newborns with or without inhibitors.

Bleed outcomes analyses will be conducted separately in all patients as well as in age-defined subgroups including newborns with or without inhibitors. Mean ABR with standard deviation and percentage of patients with zero bleeds will be reported overall and in subgroups defined by inhibitor status and age. Summary statistics will be provided overall and for the relevant subgroups.

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 30 November 2019 in order to obtain early data especially for newborns and infants.

Last Data Extraction:

The last data extraction is the date from which the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) is completely available. The planned last data extraction date is January 2022 for all age groups.

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: None

5. MILESTONES

Milestone	Planned Date
Registration of protocol in the EU PAS register	27 November 2019
First Data Extraction	November 2019
Last Data Extraction	Jan 2022
Annual report	30 Sep 2020–30 Sep 2022
Final report of study results (CSR)	30 Sep 2022
Registration of the results in the EU PAS register	30 October 2022
Publication submission	6 months after CSR

6. RATIONALE AND BACKGROUND

Hemophilia A is an X-linked recessive bleeding disorder characterized by deficiency or absence of blood coagulation factor VIII (FVIII), which leads to a lifelong bleeding tendency. It is estimated that hemophilia occurs in approximately 1:5000 newborn males. Approximately 65% of people with hemophilia A have moderate or severe forms characterized by FVIII activity levels 1%–5% or <1%, respectively, leading to frequent spontaneous bleeding events with complications, such as arthropathy, local functional deficits, hemorrhagic shock, neurocognitive defects, and death.

Primary prophylaxis with FVIII replacement therapy, consisting of intravenous infusion of FVIII 2–4 times each week starting before or after the first bleed, has proven to minimize bleeding events and complications and has become standard-of-care among pediatric patients. Although effective when optimally administered, prophylaxis with intravenous infusion can be accompanied by significant burden of treatment and can impact on the quality of life of both patients and their caregivers. Although patients on FVIII prophylaxis experience low numbers of bleeds, magnetic resonance imaging scans demonstrate progressive arthropathy in up to two-thirds of patients who receive an primary prophylaxis regimen, likely due to challenging adherence and subclinical bleeds associated with low FVIII trough levels (Ljung and Andersson 2015).

The development of neutralizing antibodies (inhibitors) against FVIII occurs in up to 30% of patients after exposure to therapeutic FVIII concentrates and represents the most common complication of these therapies. Permanent eradication of inhibitors can be achieved in 60%–80% of patients by immune tolerance induction using intensive FVIII administration (Santagostino et al. 2009; Hay and DiMichele 2012). In patients with high-titer inhibitors following re-challenge with FVIII, use of bypassing agents (BPAs) is required for the treatment and/or control of bleeding events. Unfortunately, the

hemostatic effect of bypassing agents is suboptimal, and these agents are associated with higher rate of adverse events (AEs) and treatment burden (Konkle et al. 2007; Antunes et al. 2014) compared with those of FVIII concentrates in patients without inhibitors (Manco-Johnson et al. 2013), in both children and adults.

Emicizumab (also known as Hemlibra®) is a humanized monoclonal modified immunoglobulin G4 antibody with a bispecific antibody structure. Given that emicizumab has no structural relationship to FVIII, its efficacy is not affected by the presence of FVIII inhibitors and is not expected to induce or enhance the development of inhibitors to FVIII or to other coagulation factors. Emicizumab clinical development program included the following studies enrolling children or adolescents: Study BH29992 (HAVEN 2) in 85 patients <12 years of age and 3 adolescent patients (aged 12–18 years of age) with inhibitors, as well as inclusion of adolescent patients as part of Study BH29884 (HAVEN 1; 32 patients with inhibitor, once a week [Q1W] dosing regimen), Study BH30071 (HAVEN 3; 8 patients without inhibitors, Q1W or every 2 weeks dosing regimen), and Study BO39182 (HAVEN 4; 1 patient with inhibitors and 3 patients without inhibitors, every 4 weeks dosing regimen). At the time of developing this protocol, Emicizumab is approved approximately 90 countries including the United States, European Union, Canada, China, etc. for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors. Emicizumab is also approved in the United States and 35 other countries for routine prophylaxis in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with all severity levels without inhibitor. In European Union, Emicizumab was approved for routine prophylaxis in adult and pediatric patients with severe hemophilia A (congenital factor VIII deficiency) without inhibitor on 11 March 2019.

While the results observed in the clinical trials supporting the benefit-risk assessment at the time of the marketing authorization application are compelling and demonstrate a favorable benefit-risk profile, experience with emicizumab in the pediatric population has been primarily based on pediatric patients with inhibitors. In addition, there is no clinical experience with emicizumab use in newborns (birth to Day 28 of life), who are vulnerable to development of severe bleeds. The post-approval evaluation of the drug's outcomes and utilization is vital to assessing whether the efficacy and safety profile observed in clinical trials match the real-world experience in all age groups. To address this, data collected by the European Pediatric Network for Haemophilia Management (PedNet) Registry (Appendix 1) will be extracted annually and analyzed according to the current protocol, and Annual Reports will be generated.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The main research question for this study is the safety of emicizumab use in children with hemophilia A during routine clinical care. The primary safety events of interest are

thromboembolic events (TEs), thrombotic microangiopathy (TMA), and anaphylaxis. However, all safety events collected in the PedNet registry will be reported. In addition to safety, effectiveness of emicizumab will be evaluated by the annual bleeding rate (ABR), as reported in the PedNet.

7.2 OBJECTIVES

The primary objective for this study is as follows:

- To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and inhibitor status

  Primary safety endpoints:

  Frequency and incidence of TEs, TMA, anaphylaxis

The secondary objectives for this study are as follows:

- To evaluate frequency and incidence of any adverse events reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age and inhibitor status

  Secondary safety endpoints:

  Any AEs reported to PedNet Registry

- To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and inhibitor status

  Secondary effectiveness endpoints:

  ABR for treated* bleeds and percentage of patients with zero treated bleeds

  ABR for joint bleeds, soft tissue bleeds, major bleeds, and minor bleeds

  *As per PedNET data collection, all bleeds reported are treated bleeds

8. RESEARCH METHODS

8.1 STUDY DESIGN

This is a non-interventional (NI) secondary data use Post-Authorization Safety Study (PASS) relying on data collected as part of the PedNet Registry. PedNet Registry will extract data (e.g., all variables) indicated in this protocol, perform the statistical analysis and provide results to the Marketing Authorization Holder (MAH) as aggregated report. Based on this, the MAH will generate an annual PASS report and submit it to the Pharmacovigilance Risk Assessment Committee (PRAC) and/or include the annual report in the periodical benefit risk evaluation report (PBRER) depending on the time of availability of the reports.

PedNet is a multicenter, observational research database that includes patients with FVIII/IX levels $\leq$0.025 IU/mL born after 1 January 2000 and treated in one of the participating Hemophilia Treatment Centers (HTCs). Currently 31 centers from 18 countries are participating in the Registry. The goal of the registry is to include full

cohorts of all consecutive patients diagnosed and treated in each center of which information on treatment and outcomes (e.g., inhibitor development, bleeds) is collected from the time of hemophilia diagnosis or time of first treatment. To prevent selection bias, patients referred to a center after development of inhibitors will not be included in the database.

Data included in the registry will be collected using electronic case report forms. Baseline data that pertains to mode of delivery, neonatal events, diagnostic symptoms, FVIII/IX gene mutation, and family history of hemophilia and inhibitors will also be collected. All centers will collect detailed data on treatment and outcomes (including inhibitor development and bleeds) of patients with hemophilia during the first 50 days of exposure to coagulation factor concentrate products. Following this, the centers will continue to collect information at least annually until the patient reaches the age of 18. Additional information will be collected regarding surgeries, hospitalizations, and AEs.

A similar level of detail will be collected for patients treated with emicizumab prophylaxis. When patients treated with emicizumab receive coagulation factor concentrate products, the type of the products will be recorded. It is therefore possible to evaluate the relationship between the use of FVIII/BPAs and development of TE/TMA events for patients treated with emicizumab prophylaxis.

PedNet emicizumab specific report will include patients who are treated with emicizumab. The following data will be included in the reports: number of patients treated with emicizumab, duration of emicizumab exposure, number of TE, TMA, anaphylaxis, and any other AEs, ABR for treated bleeds, percentage of zero bleeds, ABR for joint bleeds, ABR for soft tissue bleeds, ABR for major or minor bleeds, , number of patients which have used bypassing aPCC agents when treated with emicizumab, number of patients which have used FVIII products when treated with emicizumab, the number of patients used rFVII when treated with emicizumab and detailed data for patients who have developed TE, TMA or and anaphylaxis. Based on the PedNet annual report, the MAH will produce the PASS report annually with the following information grouped by age (including newborn) and status of inhibitor and/or include the results in the annual PBRER depending on the time of availability of PedNet reports:

- Number of patients exposed to emicizumab (directly from PedNet report)
- Number of patients exposed to emicizumab who experienced TE, TMA, and anaphylaxis (calculated from PedNet report)
- Proportion and incidence of each AE of TE, TMA, and anaphylaxis among patients receiving emicizumab (calculated based on information from PedNet report)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, FVIII (directly from PedNet report)
- Number of patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, FVIII, who experienced TE, TMA, and anaphylaxis (calculated from PedNet report)

- Proportion of TE and of TMA among patients exposed to emicizumab and each of the following drugs: aPCC, rFVIIa, and FVIII (calculated based on information from PedNet report)
- Number of any other AE and number of patients with any other AE (including inhibitor development, unexpected poor efficacy, local subcutaneous reactions) reported to PedNet Registry (directly from PedNet report)
- ABR for treated bleeds, percentage of zero bleeds, ABR for joint bleeds, ABR for soft tissue bleeds, ABR for major or minor bleeds (directly from PedNet report)
-

PedNet performs annual data extractions in January of each year. Following each data extraction, PedNet group will analyze the data according to this protocol and provide the MAH with Annual Emicizumab-Specific Reports.

8.2 SETTING

PedNet registry is the largest registry in the world for pediatric patients with hemophilia. Currently, 17 European countries plus Canada with approximately 31 treatment centers participate in the registry. The registry includes all age groups up to 18 and severities (FVIII <25%) which includes substantial coverage and an adequate representation of the pediatric patient population.

The following criteria describe the population eligible for this study, which will be a subset of the overall population participating in the PedNet Registry.

Inclusion criteria for inclusion in the PedNet registry:

- Diagnosis of hemophilia A
- Factor VIII activity <25%
- Treated in one of the participating centers

Additional inclusion for emicizumab-specific analysis:

- Received prophylactic treatment with emicizumab

Exclusion criteria for the PedNet registry:

- Referral to a participating HTC after development of inhibitors
- Informed consent for participation in the PedNet registry not obtained

Exclusion criteria for emicizumab-specific analysis:

- Inherited or acquired bleeding disorder other than hemophilia A

8.3 VARIABLES

Variables with pre-defined definitions included in PedNet registry are captured in the PedNet electronic case report form (eCRF). Roche will not influence any aspects of

data collection. Roche will only use the aggregated level of data provided by PedNet and provide the report to PRAC and/or include the data into PBRER.

8.3.1 Primary Safety Variables

Adverse events collected in PedNet registry are not collected according to MedDRA Classification. Most events are collected according to pre-specified lists; however, free text fields are also available for each event. For the purpose of this protocol, whenever possible they will be coded by Roche according to MedDRA Preferred Term (PT) level using the most current MedDRA version. A listing of the events reported by PedNet with the corresponding MedDRA attribution assigned will be provided

The primary safety variables are: these events will be collected for patients who receive emicizumab prophylaxis regardless whether patients received co-treatment of aPCC, rFVIIa, or FVIII

- TEs
- TMAs
- Anaphylaxis (including terms of systemic hypersensitivity, anaphylaxis, and anaphylactoid events)

8.3.2 Secondary Variables

The secondary variables for this study are as follows:

- Other AEs reported to the registry including new inhibitor development, unexpected poor efficacy, etc. Unexpected poor efficacy is included in “Other” category of AE collection in the PedNet registry eCRF.
- Bleeding event (yes/no)
- Bleed location (joint bleed, soft tissue bleed), severity (major vs. minor*)

Note Per PedNet protocol definition:

Major bleed: bleed characterized by pain, swelling, limitation of motion and failure to respond within 24 hours of treatment

Minor bleed: bleed characterized by minor pain, minimal swelling, minimal restriction of motion, resolving within 24 hours of treatment

Joint bleed: any complaint requiring treatment located in a joint

Soft tissue bleed: any complaint requiring treatment located outside the joints

- Concomitant administration of coagulation factor concentrate products (type and dose of product FVIII product, aPCC, rFVIIa) in patients receiving emicizumab.

The baseline variables for this study are as follows: baseline is defined as at the time of starting emicizumab

- Diagnosis of hemophilia A
- Exposure to emicizumab

- Age
- FVIII Inhibitor status

8.4 DATA SOURCES

PedNet is a collaboration of 31 pediatric HTCs in 18 countries (EU and Canada), providing an infrastructure for clinical research and management of children with hemophilia. The PedNet Registry started in 2003 and collects real-life data from all newly diagnosed children born with hemophilia and treated at the participating centers. Data collection through the PedNet Registry is summarized in the Study Design Section 8.1.

Data are collected through well-defined web-based Case Report Forms using a secure data-entry system capturing all aspects of hemophilia from birth to adolescence and adulthood. The database is hosted at [redacted] in the Netherlands. Centers are visited regularly for on-site data monitoring with frequency according to their size with audit of baseline information (all data entered) and bleed and medication information (10%–50% of the data entered). Data on inhibitor results are all checked and interpreted centrally. All centers will perform testing for inhibitors as advised by PedNet guidelines. All participating labs use the Nijmegen modification of the Bethesda assay with local cut off values varying between <0.3 BU/ml and <0.6 BU/ml.

In addition to monitoring of source data, numerous pre-specified logical checks are performed on the dataset. All inconsistencies or suspected errors are resolved by queries to the centers. All centers have obtained approval of their local ethical committee according to local regulations. Prior to inclusion into the registry signed informed consent is obtained from the parents. If required by local regulations, additional consent is obtained from patients after reaching 12 years of age included in the registry.

8.5 STUDY SIZE

The sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the PedNet Registry. As of January 2019, PedNet enrolled 1824 patients with hemophilia A, of which 1083 patients had severe disease and 203 patients had moderate disease. Of the patients with severe disease, 351 patients had inhibitor diagnosed between 2000 and 2019.

Assuming a constant sample size of patients with severe disease in the registry (N=1083 with severe disease, N=351 with inhibitor), and assuming that at least 15% of these patients will receive emicizumab during the 3 years of the study, the anticipated minimum sample size is expected to be n=162 for severe disease and n=53 for inhibitor disease at the end of this 3-year study. The table below presents possible sample sizes with the average adoption of the drug among these patients varies between 15%–75%

during the study. The MAH acknowledges that these estimates may change if the total number of patients enrolled in the registry changes significantly during the study time.

Table 1 Possible Sample Sizes

Emicizumab Adoption	15%	25%	50%	75%
Number of patients without inhibitor and with severe disease treated with emicizumab [a]	162	271	542	812
Number of patients with inhibitor treated with emicizumab [a]	53	88	176	263

[a] based on N=1083 patients with severe disease and N=351 with inhibitor enrolled in the PedNet registry as of January 2019

8.6 DATA MANAGEMENT

As per the PedNet registry protocol, data will be collected and updated on each regular visit to the center. The data entry environment is web based and secured by personal login and password. Forms will be completed and submitted to the central database in [redacted], The Netherlands. The data system meets GCP guidelines (ISO 9001:2000 since 2005) and is FDA compliant (21 CFR part 11).

No personal data will be provided to Roche/Genentech.

8.7 DATA ANALYSIS

The MAH will receive aggregate level data of patients treated with emicizumab from PedNet registry on an annual basis.

Based on the number of patients, number of AEs, and exposure to emicizumab provided by PedNet registry, the MAH will perform analyses of frequencies/incidence of AEs grouped by age and inhibitor status. The youngest age group will be newborn (birth to 28days). Other age groups include: <6 months, 6 months–<2 years, 2 years–<6 years, 6 years–<12 years, 12 years–18 years.

The MAH will report ABR for treated bleeds, percentages of zero bleeds, ABR for joint bleeds, soft tissue bleeds, major and minor bleeds grouped by age and inhibitor status as sent by PedNet registry. No additional analyses will be performed.

8.7.1 Safety Analyses

The primary AEs are TE, TMA, and anaphylaxis. Additional AEs including inhibitor development and unexpected poor efficacy will be included as they are collected by PedNet registry.

Adverse events collected in PedNet are not collected according to MedDRA classification. Most events are collected according to pre-specified lists; however,

free-text fields are also available for each event. Whenever possible, AEs will be reclassified by Roche according to MedDRA PT level using the most current MedDRA version.

Primary analyses: For each AE of interest (TMA, TE, and anaphylaxis), the following analysis will be performed grouped by age (including newborns) and inhibitor status:

- Annual incidence rate of the AE among patients exposed to emicizumab will be estimated as the number of patients who were treated with emicizumab and developed the AE, divided by the person years of emicizumab exposure. The numerator will be calculated using report from PedNet. PedNet will provide number of patients treated with emicizumab and emicizumab mean exposure days which will be used to calculate the person years of emicizumab exposure using the following formula. Exact binomial 95% confidence intervals will be calculated for each incidence rate.

Person years of emicizumab exposure=[number of patient exposure with emicizumab×mean emicizumab exposure time in days−number of patient exposed with emicizumab and had event×(mean emicizumab exposure time in days/2)]/365.25

Secondary analyses:

- Annual incidence proportion of AE of interest (TMA, TE, and anaphylaxis) among patients exposed to emicizumab will be estimated as the number of patients who were treated with emicizumab and developed the AE, divided by the number of patients who are exposed to emicizumab. The incidence proportion will be calculated by age group and inhibitor status.
- For each AE of interest (TMA, TE, and anaphylaxis), the following proportions will be calculated, together with the corresponding 95% confidence intervals:

  Annual incidence proportions of the AE among patients treated withemicizumab and concurrently with each of the following drugs: aPCC, rFVIIa, and FVIII product.
- Annual number and percentage of each of the other adverse events reported to PedNet will be presented. Currently, in addition to TE, TMA, and anaphylaxis, these events may include: new inhibitors, allergic reactions, local subcutaneous reaction, other AEs including unexpected poor efficacy.

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH 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. The PedNet registry is responsible for data quality assurance and quality control. All procedures including data collection, storing, monitoring, and quality assurance will be done by PedNet registry independent of the MAH following European Guidelines and the advice from the European Science Foundation. The Registry has a central coordinator and three regional coordinators with the task of data monitoring.

Every center will be visited before start of inclusion and at the closing of the Registry. Centers will be visited regularly according to their size.

No individual patient data will be transferred to the MAH.

Retention of Records

Records and documents pertaining to the conduct of this study must be retained for at least 25 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 marketing authorization holder. Written notification should be provided to the marketing authorization holder prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

TE and TMA events are recorded in the eCRF of PedNet registry as a pre-specified list. It is not possible to convert them into MedDRA PT level. For AEs recorded in the free-text fields, the MAH will code them according to MedDRA PT level using the most current MedDRA version. However, some deviation from clinical trials may occur, therefore, caution should be made when comparing results from the PedNet registry with clinical trials. This also applies for bleeding outcomes. The definitions of joint, soft tissue, major or minor bleeding could be different from clinical trials. No direct comparison should be made between results obtained from the PedNet registry and from clinical trials.

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

The PedNet registry is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects. Parents/caretakers of the patients receive written and verbal information about the registry, its aims and the consequences of their participation. Written informed consent of the parents/caregivers will be obtained. Beginning at 12 years of age, patients are able to reconsider his/her participation in the registry in some localities. The patient will receive written and verbal patient information regarding the registry and in accordance with local regulations written informed consent of the patient will be obtained at the age of 12 and older.

The MAH will only receive aggregated results; no patient level data will be received. Therefore, no informed consent in addition to the PedNet registry informed consent is needed.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

The PedNet Haemophilia Registry is a database owned and administered by the PedNet Foundation containing [anonymous] data of children with hemophilia. The PedNet Haemophilia Registry is physically placed in Baarn, The Netherlands. As of 1 December 2016, the PedNet Registry is registered on http://ClinicalTrials.gov. ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. The PedNet Registry is registered under the number NCT02979119.

The PedNet registry is conducted according to the principles of the Declaration of Helsinki (7th version, October 2013) and in accordance with the Medical Research Involving Human Subject Act (WMO). All centers have obtained approval of their local ethical committee according to local regulations.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a NI-PASS involving the use of secondary data; the reporting of adverse reactions in the form of individual case safety reports is not required.

It is assumed that safety reporting of data which are going to be extracted/analyzed as part of this study have been appropriately performed and documented at the time this data was collected through primary data collection mechanism.

Within the PedNet registry, local investigators will notify the principle investigators of all serious adverse events (SAEs), AEs, and allergic reactions (i.e. inhibitors, allergic responses, and death). Quarterly reports will be prepared of all of the reported inhibitors and will be correlated with the determinants in the PedNet registry protocol. Data reports will be sent to all participating centers. Safety reporting for emicizumab will be performed by participating centers according to National regulations issued by the appropriate authorities.

When possible, the AEs reported by PedNed registry will be classified into the appropriate level of the MedDRA classification. All AEs extracted from the PedNet

registry for this study as specified in the protocol will be summarized as part of any interim safety analyses and will be included in the final study report and final publication.

As per protocol, these aggregate summaries may include the following AE types:

- Serious Adverse Events
- Non-serious Adverse Events
- Reports of lack of efficacy

10.1 ADVERSE EVENTS

According to the International Conference of Harmonisation, 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 unfavorable 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
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

10.2 SERIOUS ADVERSE EVENTS

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 hospitalization
- 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 judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are <u>not</u> synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; the

event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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.

12. REFERENCES

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

- The European Paediatric Network for Haemophilia Management and the PedNet Haemophilia Registry