TITLE PAGE

STUDY REPORT NO. 1142641

PASS INFORMATION

TITLE:	**FINAL REPORT: EMICIZUMAB USE IN PEDIATRIC PATIENTS IN THE REAL WORLD: AN ANALYSIS OF THE PEDNET REGISTRY**
PROTOCOL NUMBER:	MO40685
VERSION NUMBER:	6.0 (FINAL)
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LINK TO STUDY RECORD IN EU PAS REGISTER:	https://catalogues.ema.europa.eu/node/3294/administrative-details
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
AUTHOR:	[redacted], PhD Principal Data Scientist, PDD F. Hoffmann-La Roche Ltd, Switzerland
DATE FINAL:	See electronic date stamp below

Date and Time(UTC)	Reason for Signing	Name
22-Aug-2025 12:01:55	Company Signatory	[redacted]

ACTIVE SUBSTANCE	B02BX06: Emicizumab
PRODUCT REFERENCE NUMBER:	EU/1/18/1271/001-6
PROCEDURE NUMBER:	EMEA/H/C/004406
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The main aim of this study is to assess the safety of emicizumab prophylaxis in children with hemophilia A in real-world conditions, among pediatric patients enrolled in the PedNet Registry. The primary objective is as follows: • To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors Primary safety endpoints: Frequency and incidence of thromboembolic events, thrombotic microangiopathy, and anaphylaxis The secondary objectives are as follows: • To evaluate the frequency and incidence of any adverse events (AEs) reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors Secondary safety endpoints: Any AEs reported to the PedNet Registry • To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors Effectiveness endpoints: • Annual bleeding rate (ABR) for all bleeds and percentage of patients with zero bleeds • ABR for joint bleeds and major bleeds • Bleeds count for all bleeds, major bleeds, minor and major joint bleeds, and minor non-joint bleeds Note: As per PedNet data collection, all bleeds reported are treated bleeds.

COUNTRIES OF STUDY POPULATION:	Countries with hemophilia treatment centers participating in the PedNet Registry: Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Norway, Portugal, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom

MARKETING AUTORISATION HOLDER

MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
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TABLE OF CONTENTS

LIST OF TABLES

1. SYNOPSIS/ABSTRACT

TITLE

Final Report: Emicizumab Use in Pediatric Patients in the Real World: An Analysis of the PedNet Registry

KEYWORDS

Emicizumab, non-interventional post-authorization safety study (NI-PASS), thromboembolic events (TEs), thrombotic microangiopathy (TMA), anaphylaxis.

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. Primary prophylaxis has proven to minimize bleeding events and complications.

Although effective when optimally administered, prophylaxis with intravenous (IV) FVIII infusion can be accompanied by significant burden of treatment with an impact on the quality of life of both patients and their caregivers. Furthermore, the development of neutralizing antibodies (inhibitors) against FVIII occurs in up to 30% of patients after exposure to therapeutic FVIII concentrates.

Emicizumab (also known as Hemlibra®) is a humanized monoclonal modified immunoglobulin G4 antibody that bridges activated factor IX (FIX) and factor X to restore the function of the missing activated FVIII needed for effective hemostasis. 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 in over 100 countries worldwide.

Two important risks have been identified with the use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: thromboembolic events (TEs) and thrombotic microangiopathy (TMA). TEs not associated with concomitant use of aPCC and anaphylaxis, anaphylactoid, or systemic hypersensitivity reactions are considered as important potential risks.

While the results observed in the clinical trials supporting the benefit-risk assessment during 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. The post-approval evaluation of the drug's outcomes and utilization is vital in assessing whether the efficacy and safety profile observed in clinical trials match the real-world experience in all age groups. The European Paediatric Network for Haemophilia Management (PedNet) Registry is a multicenter, observational research database that includes hemophilia patients with FVIII/FIX levels <25 IU/dL, born after 1 January 2000, and treated in one of the participating hemophilia treatment centers (HTCs). Data collected by the PedNet Registry are extracted and analyzed according to the study protocol, and annual reports are generated.

RESEARCH QUESTION AND OBJECTIVES

The main aim of this study is to assess the safety of emicizumab prophylaxis in real-world conditions, among pediatric patients with hemophilia A 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 during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors
  - Primary safety endpoints: frequency and incidence of TEs, TMA, and anaphylaxis

The secondary objectives for this study are as follows:

- To evaluate the frequency and incidence of any adverse events (AEs) reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors
  - Secondary safety endpoints: any AEs reported to the PedNet Registry
- To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age during emicizumab initiation, inhibitor status, and severity of hemophilia A patients without inhibitors
  - Effectiveness endpoints:
    a. Annual bleeding rate (ABR) for all bleeds* and percentage of patients with zero bleeds*
    b. ABR for joint bleeds and major bleeds
    c. Bleeds count for all bleeds, major bleeds, minor and major joint bleeds, and minor non-joint bleeds

*As per PedNet data collection, all bleeds reported are treated bleeds.

AMENDMENT AND UPDATES TO PROTOCOL

Protocol MO40685 has been amended (Protocol v2; 5 July 2023) to extend safety and effectiveness data collection to the end of the calendar year 2024 as per European Union Risk Management Plan v4.7.

In addition, the study objectives have been updated to include disease severity as a stratification factor for non-inhibitor patients. This change allows for monitoring of safety specifically for patients with moderate hemophilia A without FVIII inhibitors, which aligns with the undertaking for the recent label extension to include patients with moderate hemophilia A. Of note, no working definition for a severe bleeding phenotype was applied.

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.

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

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

PedNet performs annual data extractions in January of each year. Following each data extraction, the PedNet group analyzes the data according to the study protocol and provides the Marketing Authorization Holder with annual emicizumab-specific reports. The clinical cutoff date for this report is 31 December 2024 (inclusive).

SETTING

The PedNet Registry is the largest registry in the world for pediatric patients with hemophilia. Currently, 19 countries, comprising 17 European countries (including the United Kingdom), Israel, and Canada, with approximately 34 HTCs are participating in the Registry. The Registry

includes all age groups up to 18 years and all severities of hemophilia, including mild hemophilia A patients with FVIII <25 IU/dL. This setting provides substantial coverage and is an adequate representation of the pediatric patient population.

SUBJECT AND STUDY SIZE (INCLUDING DROPOUTS)

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

Inclusion criteria for the PedNet Registry for hemophilia A patients:

- Diagnosis of hemophilia A
- FVIII activity <25 IU/dL
- Treated in one of the participating HTCs

Additional inclusion criterion for emicizumab-specific analysis:

- Received prophylactic treatment with emicizumab

Exclusion criteria for the PedNet Registry:

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

Additional exclusion criterion for emicizumab-specific analysis:

- Inherited or acquired bleeding disorders other than hemophilia A

The final sample size depended on the approval and uptake of emicizumab in the countries with HTCs participating in the PedNet Registry.

VARIABLES AND DATA SOURCES

The primary safety variables are TEs, TMA, and anaphylaxis (including terms of systemic hypersensitivity, anaphylaxis, and anaphylactoid events).

The secondary variables for this study are other AEs reported to the Registry (including new inhibitor development and unexpected poor efficacy), bleeding events, bleed location (joint bleed or non-joint bleed), bleed severity (major or minor), and concomitant administration of coagulation factor concentrate products (type and dose of product [FVIII product, aPCC, recombinant activated factor VII]) in patients receiving emicizumab.

PedNet is a collaboration of approximately 34 pediatric HTCs in 19 countries (17 countries in Europe along with Israel 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 HTCs.

Data are collected through well-defined electronic case report forms using a secure data-entry system capturing all aspects of hemophilia from birth to adolescence and adulthood. The HTCs are visited regularly for on-site data monitoring with frequency according to their size, and audits of the baseline information and bleed and medication information are performed. Data on inhibitor results are all checked and interpreted centrally. In addition to monitoring the source data, numerous pre-specified logical checks are performed on the dataset. All inconsistencies or suspected errors are resolved by queries to the centers.

Of note, patient age in all results is defined as the patient's age during initiation of emicizumab treatment.

RESULTS

This sixth and final NI-PASS report presents interval safety data collected by the PedNet Registry from 1 January 2024 through the clinical cutoff date of 31 December 2024 (inclusive). The report also includes a comprehensive cumulative analysis of all safety data from the first recorded emicizumab exposure through this same cutoff date. Furthermore, a cumulative

analysis of bleeding events from the PedNet Registry is presented for the period from the first data extraction since emicizumab exposure (2019) up to 1 July 2023

Since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2024, 743 patients with hemophilia A received treatment with emicizumab. Of these, 578 patients with updated follow-up until 1 July 2023 were included in this PedNet report. Among them, 532 patients with a treatment period of a minimum of 6 consecutive months were included for a reliable negative binomial regression model-based ABR calculation.

In this reporting interval of 1 January 2024 to 31 December 2024, there were no TEs, TMA, or anaphylaxis AEs. No AEs were reported in patients with moderate hemophilia A without inhibitors nor in those with mild hemophilia A without inhibitors. Two patients with severe hemophilia A without inhibitors, who were aged 2 years–<6 years and 6 years–<12 years, respectively, during emicizumab initiation, reported local subcutaneous reactions.

Overall, no TMA or anaphylaxis was reported in the 578 patients through the study period. The following 15 AEs were reported cumulatively as of the final (sixth) report:

1. One case of antibodies against emicizumab reported in the second interim report
2. Two local subcutaneous reactions reported in the second interim report
3. One death unrelated to the study drug reported in the second interim report
4. One injection site reaction reported in the fourth interim report
5. One TE following sepsis and port-a-cath removal reported in the fifth interim report
6. Two local subcutaneous reactions reported in the fifth interim report
7. Two cases of redness at injection site reported in the fifth interim report
8. Three other AEs reported in the fifth interim report
9. Two local subcutaneous reactions reported in the sixth (final) report

Following a median duration of emicizumab exposure of 28.1 months (inter-quartile range: 16.6–41.9) in 578 patients, 264 patients (46%) had zero bleeds and 436 (75%) had zero joint bleeds while receiving emicizumab prophylaxis. Of the 993 bleeds reported, 277 (28%) were major bleeds and 716 (72%) were minor bleeds. Moreover, 321 (32%) were joint bleeds.

The negative binomial model-based ABR for the 532 patients with a treatment period of a minimum of 6 consecutive months was 0.7 (95% CI: 0.6–0.8) for all bleeds, 0.2 (95% CI: 0.2–0.2) for major bleeds (joint and non-joint), and 0.2 (95% CI: 0.2–0.3) for joint bleeds (major and minor).

CONCLUSION

Cumulatively, among the 578 pediatric patients with hemophilia A treated with emicizumab in the PedNet Registry up to the clinical cutoff date of 31 December 2024, one TE was reported in the fifth interim report, following sepsis and removal of an infected port-a-cath. No other cases of TEs, TMA, or anaphylaxis were observed. The observed safety profile was consistent with existing clinical trial data and other published data. No new safety signals were identified. Additionally, the efficacy profile was consistent with previously reported data, thus confirming the balance of emicizumab's benefit-risk profile in the pediatric population.

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