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STUDY REPORT NO. 1131858

PASS INFORMATION

TITLE:	**INTERIM REPORT: EMICIZUMAB USE IN PEDIATRIC PATIENTS IN THE REAL WORLD: AN ANALYSIS OF THE PedNET REGISTRY**
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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

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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 and status of inhibitor as well as by severity for patients without inhibitor Primary safety endpoints: Frequency and incidence of thromboembolic events, thrombotic microangiopathy, and anaphylaxis The secondary objectives are as follows: • To evaluate 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 and status of inhibitor as well as by severity for patients without inhibitors 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 as well as by severity for patients without inhibitor Effectiveness endpoints: • Annual bleeding rate (ABR) for treated bleeds and percentage of patients with zero treated bleeds • ABR for joint bleeds and for 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 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

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1. SYNOPSIS/ABSTRACT

TITLE

Interim Report (Version 5): Emicizumab Use in Pediatric Patients in the Real World: An Analysis of the Pediatric Network (PedNet) Registry

KEYWORDS

Emicizumab, non-interventional post-authorization safety study (NI-PASS), thromboembolic events (TE), 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 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 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: TEs and TMA. Thromboembolic events not associated with concomitant use of aPCC has been identified as an important potential risk. In addition, anaphylaxis, anaphylactoid, or systemic hypersensitivity reactions were considered important potential risks based on the class of biological drugs.

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. 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. PedNet is a multicenter, observational research database that includes hemophilia patients with FVIII/FIX levels ≤0.025 IU/mL 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 and inhibitor status as well as by severity for patients without inhibitors.
  - 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 (AEs) reported to the PedNet Registry in patients treated with emicizumab, overall and in subgroups determined by age and inhibitor status, as well as by severity for patients without inhibitors.

  - 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, as well as by severity for patients without inhibitors.
  - Effectiveness endpoints:

    Annual bleeding rate (ABR) for treated* bleeds and percentage of patients with zero treated bleeds

    ABR for joint bleeds and for major bleeds

    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, 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 that pertain 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. Additional information is collected regarding surgeries, hospitalizations, and AEs.

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 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 analyzes the data according to the study protocol and provides the MAH with annual emicizumab-specific reports. The clinical cutoff date for this report is 31 December 2023 (inclusive).

SETTING

The **Ped**iatric **Net**work (PedNet) on haemophilia management Registry is the largest Registry in the world for pediatric patients with hemophilia. Currently, 19 countries, among which 17 European countries (including the United Kingdom), Israel, and Canada with approximately 32 HTCs are participating in the Registry. The Registry includes all age groups up to 18 years and all hemophilia severities 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 inclusion in the PedNet Registry:

- Diagnosis of hemophilia A
- FVIII activity <25 IU/dL
- 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

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

As of 1 January 2024, PedNet enrolled 2408 patients with hemophilia A, of which 1557 patients had severe disease, 309 patients had moderate disease and 542 patients had mild disease. Of the patients with severe disease, 457 patients had inhibitors diagnosed and were born between January 2000 and 31 December 2023.

A total of 602 patients enrolled since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2023 have started treatment with emicizumab.

Of these, 461 patients had a minimum duration of follow-up of 6 months until 31 December 2023 and were included in this PedNet report for reliable calculation of ABR (157 patients with inhibitors [severe: 146 patients; moderate: 10 patients and mild: 1 patient], 304 patients without inhibitor [severe: 277 patients; moderate: 21 patients and mild: 6 patients]).

VARIABLES AND DATA SOURCES

The primary safety variables are TEs, TMAs, 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, unexpected poor efficacy, etc.), bleeding events, bleed location (joint bleed, non-joint bleed), bleed severity (major vs. minor) and concomitant administration of coagulation factor concentrate products (type and dose of product [FVIII product, aPCC, rFVIIa]) in patients receiving emicizumab.

PedNet is a collaboration of approximately 32 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 centers.

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. Centers are visited regularly for on-site data monitoring with frequency according to their size, and audits of baseline information and bleed and medication information are performed. 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.

RESULTS

As of 1 January 2024, PedNet enrolled 2408 patients with hemophilia A, of which 1557 patients had severe disease, 309 patients had moderate disease, and 542 patients had mild disease. Of the patients with severe disease, 457 patients had inhibitors diagnosed between January 2000 and 31 December 2023.

This fifth NI-PASS report presents cumulative bleeds data collected in the PedNet Registry from the first report of emicizumab use in the Registry (19 July 2016) up to and including the clinical cutoff date of 31 December 2023. Additionally, it presents safety data collected for the period 1 January 2023 to 31 December 2023.

A total of 602 patients enrolled since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2023 have started treatment with emicizumab (225 patients with inhibitors [severe: 213 patients; moderate: 10 patients, and mild: 2 patients] and 377 patients without inhibitors [severe: 348 patients; moderate: 23 patients and mild: 6 patients]).

Of these, 461 patients had a minimum duration of follow-up of 6 months until 31 December 2023 and were included in this PedNet report (157 patients with inhibitors [severe: 146 patients; moderate: 10 patients and mild: 1 patient], 304 patients without inhibitors [severe: 277 patients; moderate: 21 patients and mild: 6 patients]).

One patient with severe disease and without inhibitor in the 6 months to <2 years age group, reported TE (preceded by sepsis and removal of infected port-a-cath). No patient reported TMA or anaphylaxis.

An AE of local subcutaneous reaction was reported in one patient <28 days and in one patient in the 6 months to <2 years age group. Two patients in the age group of 6 years to <12 years reported allergic reaction (redness at injection site). Three patients (one patient in the age group of 6 months to <2 years, one patient in the age group 2 years to <6 years, and one patient in the age group of 6 years to <12 years) reported other AE (i.e., AEs other than TMA, or anaphylaxis). Of these one AE of local subcutaneous reaction and one other AE were reported in patients with severe disease and with an inhibitor the remaining AEs (two allergic reactions, one local subcutaneous reaction and two other AEs) were reported in patients with severe disease and without an inhibitor. Of note, the age for all the patients that reported AEs was the age at which emicizumab was started.

Twenty-one patients with moderate hemophilia A without inhibitor and 6 patients with mild hemophilia A without inhibitors are included in this year's report. None of them reported an AE in the study period.

Following a median duration of emicizumab exposure of 21.55 months (intra-quartile range [IQR]: 10.78 - 33.74), the negative binomial model-based ABR for treated bleeds was 0.69 (95% CI: 0.60 - 0.80). A total of 236 patients (51%) had zero treated bleeds while receiving emicizumab prophylaxis. Of 590 treated bleeds reported, 181 (31%) were joint bleeds, 163 (28%) were major bleeds and 427 (72%) were minor bleeds. The negative binomial model-based ABR was 0.21 (95% CI: 0.17 - 0.27) and 0.20 (95% CI: 0.16 - 0.26) for treated joint bleeds and major bleeds; respectively.

CONCLUSION

A total of 602 patients enrolled since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2023 have started treatment with emicizumab. Of these, 461 patients had median treatment duration of 21.55 months (IQR: 10.8 - 33.7).

None of the pediatric patients with hemophilia A treated with emicizumab at centers participating in the PedNet Registry reported TMA or anaphylaxis events.

The first TE (preceded by sepsis and removal of infected port-a-cath) has been reported in a patient with severe disease without inhibitor in the 5th year report. .No other TE events have been recorded.

The efficacy and safety profile reported in the study is consistent with previous findings thus further reinforcing the positive benefit-risk profile of the molecule.

The majority of the reported treated bleeds were minor non-joint bleeds. Overall, 31.7% (146/461) of patients had FVIII inhibitors and the inhibitor population had a much longer follow up (median 28.34 months [IQR: 10.35 - 42.51]) vs the non-inhibitor population (median

13.4 months [IQR: 6.8 - 21.4]). This difference is likely due to the timing of approvals for the inhibitor and non-inhibitor populations.

This is the fifth report for Study MO40685 and data is still evolving. A full assessment will be reported in the final clinical study report in September 2025. The observed safety profile was consistent with existing clinical trial data and other published data. No new safety signals were identified. Additionally, the bleeding profile was also consistent with previously reported data thus confirming the emicizumab benefit risk balance established in the pediatric population.

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