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STUDY REPORT NO. 1127290

PASS INFORMATION

TITLE:	**INTERIM REPORT: EMICIZUMAB USE IN PEDIATRIC PATIENTS IN THE REAL WORLD: AN ANALYSIS OF THE PEDNET REGISTRY**
PROTOCOL NUMBER:	MO40685
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STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
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DATE FINAL:	See electronic date stamp below

STUDY REPORT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
29-Sep-2023 14:53:18	Company Signatory	[redacted]

ACTIVE SUBSTANCE	B02BX06: Emicizumab
PRODUCT REFERENCE NUMBER:	EU/1/18/1271/001-5
PROCEDURE NUMBER:	EMEA/H/C/004406
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The main aim of this study is to assess 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 AUTHORISATION HOLDER

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1. SYNOPSIS/ABSTRACT

Title

Interim Report (Version 4): 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 (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 to 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 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
  - Secondary 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 EU RMP v.4.7. In addition, the study objectives have been updated to include disease severity as a stratification factor for noninhibitor patients. This change will allow reporting of the safety of emicizumab in patients with moderate hemophilia A without FVIII inhibitors. This change will be implemented starting from the next annual report generated by PedNet and therefore data on moderate patients without inhibitor, already included in this interim report, will be reported as a separate category starting from next interim report.

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 Marketing Authorisation Holder with annual emicizumab-specific reports. The clinical cutoff date for this report is 31 December 2022 (inclusive).

Setting

The **Ped**iatric **Net**work on haemophilia management (PedNet) 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 (FVIII $<$ 25 IU/dL), which provides substantial coverage and is an adequate representation of the pediatric patient population.

Patients 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 will depend on the approval and uptake of emicizumab in the countries with centers participating in the PedNet Registry. As of 1 January 2023, PedNet enrolled 2302 patients with hemophilia A, of which 1491 patients had severe disease and 294 patients had moderate disease. Of the patients with severe disease, 445 patients had inhibitors diagnosed between 2000 and 2022.

A total of 428 patients with hemophilia A enrolled since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2022 have started treatment with emicizumab. Of these, 372 patients had a minimum duration of follow-up of 6 months until 31 December 2022 and were included in this PedNet report for reliable calculation of ABR (140 patients with inhibitors, 231 patients without inhibitors, and one patient with unknown inhibitor status).

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 2023, PedNet enrolled 2302 patients with hemophilia A, of which 1491 patients had severe disease, 294 patients had moderate disease, and 517 patients had mild hemophilia A. Of the patients with severe disease, 445 patients had inhibitors diagnosed between 2000 and 2022.

This fourth 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 2022. Additionally, it presents safety data collected for the period 1 January 2022 to 31 December 2022.

A total of 428 patients enrolled since the beginning of the PedNet Registry have started treatment with emicizumab. Of these, 372 patients had a minimum follow-up of six monthsuntil 31 December 2022 and were included in this PedNet report for reliable calculation of ABR (140 patients with inhibitors, 231 patients without inhibitors, and one patient with unknown inhibitor status).

No patients reported TE, TMA, or anaphylaxis during this reporting period. One patient from age group 29 days–<6 months reported an AE of injection site reaction. This AE occurred in 2021 but was reported in 2022. No other AEs were reported during the reporting period between 1 January 2022 to 31 December 2022.

Following a median duration of emicizumab exposure of 15.7 months (intra-quartile range: 7.2–25.2) the ABR for treated bleeds was 0.83 (95% Confidence Interval (CI): 0.7–1.0) and 51% of patients did not report any treated bleeds. Of the 468 treated bleeds reported, 126 were joint bleeds, and 97 were major bleeds. The majority (60%) of the treated bleeds reported were minor non-joint bleeds. The ABRs were 0.24 (95% CI: 0.2–0.3) and 0.16 (95% CI: 0.1–0.2) for treated joint bleeds and treated major bleeds respectively.

Conclusion

None of the pediatric patients with hemophilia A treated with emicizumab at centers participating in the PedNet Registry reported TE, TMA, or anaphylaxis events. Except for one patient from age group 29 days–<6 months who reported an injection site reaction, no other AEs were reported during the reporting period (1 January 2022 to 31 December 2022). This AE occurred in 2021 but was reported in 2022. Most of the reported treated bleeds were minor non-joint bleeds. Overall, 37.6% of patients had FVIII inhibitors (140/372), and the inhibitor population had a much longer follow up (median 22.9 months [IQR 8.8–35.7]) 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 noninhibitor populations.

This is the fourth report for Study MO40685 and data are still evolving. A full assessment will be made at the final analysis in September 2025. The observed safety profile was consistent with existing clinical trial data and other published data. No new safety signals were identified and efficacy was also in line with prior data.

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