

## TITLE PAGE

### STUDY REPORT NO. 1117001

#### PASS INFORMATION

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

#### STUDY REPORT APPROVAL

<b>Date and Time(UTC)</b>	<b>Reason for Signing</b>	<b>Name</b>
28-Sep-2022 13:44:35	Company Signatory	[REDACTED]

<b>ACTIVE SUBSTANCE</b>	B02BX06: Emicizumab
<b>PRODUCT REFERENCE NUMBER:</b>	EU/1/18/1271/001-4
<b>PROCEDURE NUMBER:</b>	EMA/H/C/004406
<b>JOINT PASS:</b>	No
<b>RESEARCH QUESTION AND OBJECTIVES:</b>	<p>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.</p> <p>The primary objective is as follows:</p> <ul style="list-style-type: none"> <li>To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and inhibitor status</li> </ul> <p>Primary safety endpoints:</p> <p>Frequency and incidence of thromboembolic events, thrombotic microangiopathy, and anaphylaxis</p> <p>The secondary objectives are as follows:</p> <ul style="list-style-type: none"> <li>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</li> </ul> <p>Secondary safety endpoints:</p> <p>Any adverse events reported to PedNet Registry</p> <ul style="list-style-type: none"> <li>To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and inhibitor status</li> </ul> <p>Secondary efficacy endpoints:</p> <ul style="list-style-type: none"> <li>Annual bleeding rate (ABR) for treated bleeds and percentage of patients with zero treated bleeds</li> <li>ABR for joint bleeds, soft tissue bleeds, major bleeds, and minor bleeds</li> </ul>

<b>COUNTRIES OF STUDY POPULATION:</b>	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
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**MARKETING AUTHORISATION HOLDER**

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## 1. **SYNOPSIS/ABSTRACT**

### **TITLE**

Interim Report (Version 3): 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<sup>®</sup>) 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 as potential safety 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. In addition, there is limited clinical experience with emicizumab in newborns (birth to 28 days old) and infants (<1 year old), who are vulnerable to development of severe bleeds including intracranial hemorrhage. 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  $\leq 0.025$  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

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

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:

Annual bleeding rate (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

## **AMENDMENT AND UPDATES TO PROTOCOL**

None

## **STUDY DESIGN**

This is a non-interventional, secondary data use Post-Authorization Safety Study 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 2021 (inclusive).

## **SETTING**

The 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 33 HTC's participating in the registry. The registry includes all age groups up to 18 years and all severities (FVIII < 25%) which includes 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%
- 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 2022, PedNet enrolled 2148 patients with hemophilia A, of which 1411 patients had severe disease and 263 patients had moderate disease. Of the patients with severe disease, 419 patients had inhibitors diagnosed between 2000 and 2021.

A total of 266 patients enrolled since the beginning of the PedNet Registry up until the clinical cutoff date of 31 December 2021 have started treatment with emicizumab. Of these, 216 patients had updated follow-up data until 31 December 2021 and were included in this PedNet report (80 patients with inhibitors, 132 patients without inhibitors, and 4 patients with unknown inhibitor status). This reflects a > 50% adoption rate of the drug as estimated by sample size projections in 2019.

## **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, and bleed location (joint bleed, soft tissue bleed) and severity (major vs. minor).

PedNet is a collaboration of approximately 33 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**

This third 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 2021. Additionally, it presents safety data collected for the period 1 January 2021 to 31 December 2021.

A total of 266 patients enrolled since the beginning of the PedNet Registry have started treatment with emicizumab. Of these, 216 patients had updated follow-up data until 31 December 2021 and were included in this PedNet report (80 patients with inhibitors, 132 patients without inhibitors, and 4 patients with unknown inhibitor status).

No patients reported TE, TMA or anaphylaxis during the reporting period. No other AEs were reported during the reporting period up to and including 1 January 2021 to 31 December 2021.

Following a median duration of emicizumab exposure of 14.39 months (intra-quartile range: 9.46–22.34) the ABR for treated bleeds was 1.19 (95% Confidence Interval (CI): 0.98–1.45) and 45% of patients did not report any treated bleeds. Of the 378 treated bleeds reported, 96 were joint bleeds and 54 were major bleeds. The majority (65%) of the treated bleeds reported were minor non-joint bleeds. The ABRs were 0.32 (95% CI: 0.23–0.45) and 0.18 (95% CI: 0.12–0.25) 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. No other AEs were reported during the reporting period (1-Jan-2021 to 31-Dec-2021). Most of the reported treated bleeds were minor non-joint bleeds. The majority of patients had FVIII inhibitors 132/216, and the inhibitor population had a much longer FU (median 22.98 months (IQR 16.89–31.61) vs median 11.56 months (IQR 6.37–15.74). This difference is likely due to the timing of approvals for the inhibitor and non-inhibitor populations.

This is the third 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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