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STUDY REPORT NO. 1139927

PASS INFORMATION

TITLE:	INTERIM REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY
PROTOCOL NUMBER:	GO40162
VERSION NUMBER:	6.0
EU PAS REGISTER NUMBER:	EUPAS23177
LINK TO STUDY RECORD IN EU PAS REGISTER:	Not applicable
STUDIED MEDICINAL PRODUCT:	Emicizumab (HEMLIBRA®, ACE910, RO5534262)
AUTHOR:	[redacted] Principal Data Scientist PDD RWDS; Pharmaceutical Division F. Hoffmann-La Roche Ltd., Switzerland
DATE FINAL:	See electronic signature below

Date and Time(UTC)	Reason for Signing	Name
17-Jun-2025 14:02:13	Company Signatory	[redacted]

ACTIVE SUBSTANCE	Emicizumab (ATC code: B02BX06)
PRODUCT REFERENCE NUMBER:	Not applicable
PROCEDURE NUMBER:	EMEA/H/C/004406
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The main goal of this study is to assess the incidence of thromboembolism (TE), thrombotic microangiopathy (TMA), and anaphylaxis in real-world conditions, in patients exposed to emicizumab The primary objective for this study is as follows: • To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products The secondary objectives for this study are as follows: • To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and concomitantly with each of the following drugs: activated prothrombin complex concentrate (aPCC), recombinant activated factor VII (rFVIIa), and factor VIII (FVIII) products • To describe individual cases of TE and TMA based on available information • To summarize the frequency of other adverse events collected by European Haemophilia Safety Surveillance (EUHASS) in patients exposed to emicizumab • To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information
COUNTRIES OF STUDY POPULATION:	Countries with hemophilia centers participating in the EUHASS Registry: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and United Kingdom.

MARKETING AUTHORIZATION HOLDER

MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
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1. SYNOPSIS/ABSTRACT

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SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUROPEAN HAEMOPHILIA SAFETY SURVEILLANCE (EUHASS) PHARMACOVIGILANCE REGISTRY

Keywords

Emicizumab, EUHASS, non-interventional post-authorization safety study (NI-PASS), thromboembolism (TE), thrombotic microangiopathy (TMA).

Rationale and Background

Emicizumab (also known as Hemlibra®, ACE910, and RO5534262) is a humanized monoclonal modified immunoglobulin G4 antibody that bridges activated factor IX and factor X to restore the function of missing activated factor VIII (FVIII) needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors. As of June 2025, emicizumab is approved in approximately 125 countries worldwide in patients with hemophilia A with FVIII inhibitors and is approved in approximately 119 countries worldwide for the expanded indication to include patients with hemophilia A without FVIII inhibitors, including approval in the United States, Japan, and the European Union. Two important risks have been identified with the use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: TE and TMA. In addition, one important risk of loss of efficacy due to anti-emicizumab antibodies has been identified with the use of emicizumab alone. Anaphylaxis, anaphylactoid, and severe systemic hypersensitivity reaction are considered as potential safety risks based on the class of biological drugs.

In order to better assess the incidence of TE, TMA, anaphylaxis, and other adverse events (AEs) the Marketing Authorization Holder (MAH) will use information collected by the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program. EUHASS provides the MAH an emicizumab-specific annual report which is used to calculate the incidence of TE, TMA, anaphylaxis, other AEs and individual cases of “unexpected poor efficacy’’.

Research Question and Objectives

The main goal of this study is to assess the incidence of TE, TMA, and anaphylaxis under real-world conditions in patients exposed to emicizumab.

The primary objective for this study is as follows:

- To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products

The secondary objectives for this study are as follows:

- To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and concomitantly with each of the following drugs: aPCC, recombinant activated factor VII (rFVIIa), and FVIII product
- To describe individual cases of TE and TMA
- To summarize the frequency of other AEs collected by EUHASS in patients exposed to emicizumab
- To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information

Amendment and Updates to Protocol

The first version of the protocol was issued on 29 January 2018. There were three subsequent protocol amendments on 7 September 2018 (Version 2), 8 February 2019 (Version 3) and 20 December 2023 (Version 4). There were no updates to the protocol in the current reporting period.

Study Design

Study GO40162 is a cohort surveillance study based on data provided in the EUHASS emicizumab-specific annual report.

Setting

European Haemophilia Safety Surveillance is a pharmacovigilance program dedicated to monitor the safety of treatments for people with inherited bleeding disorders across Europe. It is led by European Association for Haemophilia and Allied Disorders (EAHAD) and coordinated by Prof. Dr. [redacted]. Its activities are overseen by an independent Steering Committee. Since its initiation in 2008, EUHASS is used by pharmaceutical companies to conduct post-approval authorization studies. At the time of the EUHASS report in 2023, 95 participating centers in 28 countries reported information on all the patients they treated, thus minimizing selection bias.

Patients and Study Size (Including Dropouts)

Data from patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS Registry are collected.

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

Variables and Data Sources

The primary variables for this study are as follows:

- TE events
- TMA events
- Anaphylaxis events
- Exposure to emicizumab

The secondary variables for this study are as follows:

- Transfusion transmitted infections
- New inhibitors (antibodies against the coagulation factor)
- Allergic and other acute reactions, with the exception of anaphylaxis
- New malignancy diagnosis
- Death
- Unexpected poor efficacy
- Other AEs possibly related to concentrate
- Exposure to emicizumab, without replacement factor products in the same calendar year
- Exposure to both aPCC and emicizumab in the same calendar year
- Exposure to both rFVIIa and emicizumab in the same calendar year
- Exposure to both FVIII and emicizumab in the same calendar year

Variables are captured using information from standard patient management. No additional evaluations are done as a consequence of participation in the EUHASS Registry or as a consequence of this study.

Results

From 1 January 2023 to 31 December 2023, a total of 2208 patients received emicizumab, either as a standalone treatment or in combination with coagulation factor products.

During this reporting period, 7 AEs were reported to EUHASS, all patients were males and diagnosed with hemophilia A. A description of the AEs is provided below:

- Coronary stenosis ($n = 1$): Reported by a 54-year-old immediately after dosing. The serious adverse event (SAE) was reported as thromboembolic event to EUHASS database however, limited information pertaining to clinical course was available to verify the event.

- Rash[1] (n = 1): Experienced by a 10-month-old treated with emicizumab along with other FVIII. The rash appeared within 5 minutes of dosing, resolved, and was considered by the investigator to be definitely related to concentrate/non-factor replacement (NFR)[2].
- First occurrence of inhibitor development (n = 2): Patients aged between 1 and 15 years treated with emicizumab along with other FVIII.
- Recurrence of FVIII inhibitors (n = 2) occurred in patients aged between 8 and 55 years treated with emicizumab alone.
- Recurrence of FVIII inhibitors (n = 1): Patient aged between 6 and 55 years treated with emicizumab along with other FVIII.

No instances of TMA or anaphylaxis were reported during the current reporting period.

Conclusion

During the reporting interval from 1 January 2023 to 31 December 2023, a total of 2208 patients were treated with emicizumab alone or emicizumab in combination with coagulation factor products. Seven AEs were reported however limited information was received for the reported events, and no safety impact could be drawn from this data.

Over the full study period (from earliest use of emicizumab at centers participating in the EUHASS Registry in 2017 up to 31 December 2023, the sum of person-years exposed to emicizumab, either alone or with coagulation factor products, is estimated to be 7913), 43 AEs have been reported, of which 7 were TEs and no TMA or anaphylaxis events were reported.

It is concluded that the observed safety profile for emicizumab is acceptable and consistent with other published data. No new safety signals were identified upon reviewing the current data.

The final clinical study report is expected to be completed by June 2026, and the sponsor will provide updates as the data evolves.

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[1] During this reporting period, allergic and acute reactions were initially reported for both emicizumab alone and for emicizumab with other FVIII. However, EUHASS confirmed that the event attributed to emicizumab alone was an erroneous duplicate entry and correctly pertains to the emicizumab + FVIII category.

[2] In cases involving multiple drugs, EUHASS does not provide the identification of which drug attributed to specific events. This is limitation of EUHASS data collection process.