TITLE PAGE

STUDY REPORT NO. 1155118

PASS INFORMATION

TITLE:	**FINAL REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
VERSION NUMBER:	7.0 (Final)
HMA EMA RWD CATALOGUE NUMBER (formerly EU PAS Register Number):	EUPAS23177
LINK TO STUDY RECORD IN HMA EMA RWD CATALOGUE:	Not applicable
STUDIED MEDICINAL PRODUCT{S}:	Emicizumab (HEMLIBRA®, ACE910, RO5534262)
AUTHOR:	[redacted] PDD RWDS; Pharmaceutical Division F. Hoffmann-La Roche Ltd., Switzerland
DATE FINAL:	See electronic date stamp on signature page

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, 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 thromboembolic events (TEs), 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 TEs 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
COUNTRY OR 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 AUTORISATION HOLDER(S)

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TABLE OF CONTENTS

LIST OF TABLES

1. SYNOPSIS/ABSTRACT

TITLE

FINAL REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY

KEYWORDS

Emicizumab, European Haemophilia Safety Surveillance (EUHASS), non-interventional post-authorization safety study (NI-PASS), thromboembolism, thrombotic microangiopathy (TMA), anaphylaxis.

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 November 2025, emicizumab is approved in approximately 126 countries worldwide in patients with hemophilia A with FVIII inhibitors and is approved in approximately 121 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 identified risks have been associated with the use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: thromboembolic events (TEs) and TMA. Thromboembolic events (TEs) in the absence of concomitant aPCC is considered as an important potential risk. In addition, one important identified risk of loss of efficacy due to anti-emicizumab antibodies has been identified with the use of emicizumab alone. Anaphylaxis, anaphylactoid, severe systemic hypersensitivity reaction, and life-threatening bleeding due to the misinterpretation of standard coagulation tests are considered as important potential safety risks.

In order to better assess the incidence of TEs, TMA, anaphylaxis, and other adverse events (AEs), the Marketing Authorization Holder (MAH) has used information collected by the EUHASS pharmacovigilance program. EUHASS provides the MAH an emicizumab-specific annual report which is used to calculate the incidence of TEs, TMA, anaphylaxis, other AEs and individual cases of "unexpected poor efficacy''. This document serves as the final Clinical Study Report (CSR) for Study GO40162.

RESEARCH QUESTION AND OBJECTIVES

The main goal of this study is to assess the incidence of TEs, 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 TEs, 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 TEs and TMA in patients exposed to emicizumab alone and concomitantly with each of the following drugs: aPCC, recombinant activated factor VII (rFVIIa), and FVIII products
- To describe individual cases of TE and TMA based on available information
- 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

The EUHASS program is an investigator-led initiative originally coordinated by Prof. Dr. [redacted] and currently led by Dr. [redacted] 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 2024, 94 participating centers in 28 countries reported information on all the patients they treated, thus minimizing selection bias.

SUBJECT AND STUDY SIZE (INCLUDING DROPOUTS)

The study population consists of patients with congenital hemophilia A treated with emicizumab at centers participating in the EUHASS Registry.

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:

- TEs
- 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/non-factor replacement (NFR)
- 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

This seventh and final NI-PASS report presents interval safety data collected by the EUHASS Registry from 1 January 2024 through the clinical cut-off date of 31 December 2024 (inclusive).

The report also includes a comprehensive cumulative analysis of all safety data from the first recorded emicizumab exposure (2017) through this same cut-off date.

From 1 January 2024 to 31 December 2024, a total of 2,328 patients were treated with emicizumab alone or emicizumab in combination with coagulation factor products.

Nine AEs were reported to EUHASS during this reporting period and details are provided below:

- **Thrombosis (n=6):** Reported events included transient ischemic attack (TIA; n=2), myocardial infarction (n=1), coronary stenosis (n=1), hepatic artery thrombosis (n=1), and thrombotic stroke (n=1). These events were recorded as serious adverse events (SAEs); however, limited information pertaining to the clinical course was available to evaluate these events.
- **First occurrence of inhibitor development (n=2):** Two patients experienced a first occurrence of FVIII inhibitors. One of these cases involved a patient with severe Hemophilia A using emicizumab in combination with Recombinant Standard-half-life Factor VIII. No additional information was reported for the second patient.
- **Recurrence of FVIII inhibitors (n=1):** One patient reported a recurrence of FVIII inhibitors This case involved a patient with severe hemophilia A using emicizumab with Recombinant Extended-half-life Factor VIII.

No instances of TMA, anaphylaxis or allergic/acute reactions were reported during the current reporting period.

Cumulatively, from the earliest use of emicizumab in 2017 through the 31 December 2024 cut-off date, the sum of person-years exposed to emicizumab, either alone or with coagulation factor products, is estimated to be 9,909 person-years, with 48 AEs reported. This includes 13 patients under 'thrombosis' category (age range: 1–78 years), 15 allergic or acute reactions in 12 patients (age range: 10 months–55 years), 8 first-occurrence of inhibitor development (age range: 1–43 years), and 12 inhibitor recurrences (age range: 6–55 years). No instances of TMA and anaphylaxis were reported cumulatively. The crude incidence rate for TE was calculated as 1.31 per 1,000 person-years, assuming full-year exposure for all patients.

DISCUSSION

This final report for Study GO40162 summarizes the findings from EUHASS pharmacovigilance program, describing the incidence of TEs, TMA, anaphylaxis, and other AEs in patients treated with emicizumab between 2017 and2024. During the 2024 reporting period, 2,328 patients were treated, with 9 reported AEs including 6 events under the category of thrombosis and 3 inhibitor events. Thirteen TEs were reported cumulatively (age ranged from 1–78 years), including two reports of coronary stenosis; however, limited information prevented confirmation of thromboembolism in these two cases. Of the 13 total TEs on record, 6 were reported in 2024 reporting period All these events occurred in older adult males ages from 52 to 77 years, suggesting that advancing age may increase thrombotic risk. No TMA or anaphylaxis were reported during this reporting interval and throughout the overall study duration. Total 15 allergic or acute reactions, 8 first-occurrence inhibitor developments, and 12 inhibitor recurrences were reported cumulatively.

Based on the limited information provided in the EUHASS annual reports, it is not possible to make a comprehensive assessment regarding specific reported events; however, the observed safety profile is in line with published data from clinical trials and post-marketing experience, and no new safety signals or patterns of adverse events were identified.

CONCLUSION

This final report concludes the observation of emicizumab within the EUHASS Registry specific to Study GO40162. Throughout the study duration, the observed safety profile of emicizumab remained consistent with established clinical data, and no new safety signals were identified. Notably, no cases of TMA or anaphylaxis were reported during the overall study duration. Consistent with the findings from pivotal clinical trials, the study data confirm that the positive benefit-risk balance of emicizumab for the treatment of hemophilia A remains unchanged.

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