TITLE PAGE

STUDY REPORT NO. 1115568

PASS INFORMATION

TITLE:	**INTERIM REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
VERSION NUMBER:	3.0
EU PAS REGISTER NUMBER:	EUPAS23177
LINK TO STUDY RECORD IN EU PAS REGISTER:	n/a
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
AUTHOR:	[redacted] Senior Data Scientist, RWD oncology PHC Data Science; Pharmaceuticals Division F. Hoffmann-La Roche Ltd., Switzerland
DATE FINAL:	See electronic date stamp below

Date and Time(UTC)	Reason for Signing	Name
01-Jul-2022 14:25:16	Company Signatory	[redacted]

ACTIVE SUBSTANCE	B02BX06: Emicizumab
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 and treated at centers participating in the European Haemophilia Safety Surveillance System (EUHASS) registry. 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 replacement 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 in combination 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. • To summarize the frequency of other adverse events collected by 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 haemophilia centers participating in the EUHASS registry: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and United Kingdom

MARKETING AUTORISATION HOLDER(S)

MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	[redacted] c/o Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

TABLE OF CONTENTS:

LIST OF TABLES

1. SYNOPSIS/ABSTRACT

Title

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

Keywords

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

Rationale and Background

Emicizumab (also known as Hemlibra®, ACE910, and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) 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 haemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors. As of May 2022, emicizumab is approved in approximately 108 countries worldwide in patients with haemophilia A with FVIII inhibitors, and in approximately 96 countries worldwide for the expanded indication to include patients with haemophilia A without factor VIII inhibitors, including approval in the US, Japan, and the EU. Two important risks have been identified with the use of activated prothrombin complex concentrate (aPCC) in patients treated with emicizumab prophylaxis: thromboembolic events (TE), thrombotic microangiopathy (TMA), and one important risk of loss of efficacy due to anti-emicizumab antibodies has been identified with the use of emicizumab alone. In addition, anaphylaxis, anaphylactoid reactions, and hypersensitivity were considered as potential safety risks based on the class of biological drugs.

In order to better assess the incidence of TE, TMA, and anaphylaxis, the Sponsor will use information collected by the EUHASS pharmacovigilance program. EUHASS will provide the Sponsor with an emicizumab-specific annual report whose findings will be used to calculate the incidence of the TE, TMA, and anaphylaxis.

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 based on available information
- To summarize the frequency of other adverse events 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 14 June 2017. There were two subsequent protocol amendments on 7 September 2018 (Version 2) and 8 February 2019 (Version 3).

Study Design

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

Setting

EUHASS is a pharmacovigilance program dedicated to monitoring the safety of treatments for people with inherited bleeding disorders in Europe. It is investigator-led, coordinated from University of Sheffield, and its activities are overseen by an independent Steering Committee. At the start of the study, 86 participating centers in 27 countries report information on all the patients they treat, thus minimizing selection bias. Since its initiation in 2008, EUHASS has been used by pharmaceutical companies to conduct post-approval authorization studies.

Patients and Study Size (Including Dropouts)

Patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS registry were selected.

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

Until this reporting period with clinical cutoff date (31 December 2020) 832 patients were treated with emicizumab alone, 56 patients were treated with emicizumab and NovoSeven, 96 patients were treated with emicizumab and other FVIII (other than Obizur), 1 patient was treated with emicizumab and FEIBA, and 22 patients were treated with emicizumab and tranexamic acid.

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 adverse events 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

During this reporting period (1 January 2020 to 31 December 2020), 832 patients were treated with emicizumab alone, 56 patients were treated with emicizumab and NovoSeven, 96 patients were treated with emicizumab and other FVIII (other than Obizur), 1 patient was treated with emicizumab and FEIBA, and 22 patients were treated with emicizumab and tranexamic acid. There were no TE, TMA, or anaphylaxis events during this reporting period.

From 1 January 2020 - 31 December 2020, three adverse events were reported:

- A 40-year-old male with a diagnosis of hemophilia A reported a rash 1 hour after dosing which resolved and was considered by the investigator to be definitely related to emicizumab.

- A 55-year-old male with a diagnosis of hemophilia A reported a rash 12 hours after dosing which resolved and was considered by the investigator to be probably related to emicizumab.
- A 26-year-old male with a diagnosis of severe hemophilia A treated with emicizumab had a recurrence of FVIII inhibitors.

From the earliest use of emicizumab in 2017 to 31 December 2020, 1328 patients were treated with emicizumab alone, 131 patients were treated with emicizumab and NovoSeven, 138 patients were treated with emicizumab and FVIII (other than Obizur), 8 patients were treated with emicizumab and FEIBA, and 22 patients were treated with emicizumab and tranexamic acid. Nine adverse events (AEs) were reported, of which 4 were TEs and none were TMA or anaphylaxis events.

Conclusion

Of the patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS registry during this reporting period (832 patients treated with emicizumab alone, 56 patients treated with emicizumab and NovoSeven, 96 patients treated with emicizumab and other FVIII (other than Obizur), 1 patient treated with emicizumab and FEIBA, and 22 patients treated with emicizumab and tranexamic acid), 3 reported an AE. Two patients treated with emicizumab reported an allergic and other acute reaction (Preferred Term: both rash) and 1 patient had a recurrence of FVIII inhibitors. There were no TE, TMA, or anaphylaxis events during this reporting period. Based on a review of the available data to date, the safety profile of emicizumab without aPCC/FEIBA in patients with inherited bleeding disorders is favorable.

Based on the review of currently available data, no new safety signal was detected.

This is the third annual report for Study GO40162 and data are still evolving. A full assessment will be made at the final analysis, planned for June 2024. However, a favorable safety profile was observed that is in line with other published data.

Marketing Authorization Holder

Roche Registration GmbH

Emil-Barrell-Strasse 1

79639 Grenzach-Wyhlen

Germany

Names and Affiliations of Principal Physicians

Professor [redacted] MA, MB BS, MD, FRCP, FRCPath

Professor of Haemostasis & Thrombosis

Department of Infection, Immunity and Cardiovascular Disease

The Medical School, University of Sheffield