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STUDY REPORT NO. 1102465

PASS INFORMATION

TITLE:	**INTERIM REPORT: SURVEILLANCE OF EMICIZUMAB-TREATED PATIENTS: AN ANALYSIS OF THE EUHASS PHARMACOVIGILANCE REGISTRY**
PROTOCOL NUMBER:	GO40162
VERSION NUMBER:	1.0
EU PAS REGISTER NUMBER:	EUPAS23177
LINK TO STUDY RECORD IN EU PAS REGISTER:	n/a
STUDIED MEDICINAL PRODUCT:	Emicizumab (RO5534262, ACE910, HEMLIBRA®)
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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 to 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 hemophilia 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 AUTHORISATION HOLDER(S)

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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 hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors. As of May 2020, emicizumab is approved in over 90 countries worldwide in patients with hemophilia A with FVIII inhibitors, and in approximately 75 countries worldwide for the expanded indication to include patients with hemophilia 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) and thrombotic microangiopathy (TMA). Important potential risks include immunogenicity. One patient developed an anti-drug antibody (ADA) to emicizumab with neutralizing potential that led to loss of clinical efficacy and subsequent resumption on prior therapy without any untoward events. In addition, anaphylaxis, anaphylactoid, or systemic hypersensitivity reactions 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 European Haemophilia Safety Surveillance System (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. The 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 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. Based on the number of patients with hemophilia A participating in the EUHASS registry and the expected uptake of emicizumab, the Sponsor estimated that EUHASS will provide data on at least 680 patients treated with emicizumab by the year 2022.

This reporting period, with data to the end of 2018, includes 173 patients reported as treated with emicizumab.

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

In 2017, a total of 25 patients were treated with emicizumab. In 2018, a total of 148 patients were treated with emicizumab, including 23 patients who were treated with emicizumab and NovoSeven, 9 patients who were treated with emicizumab and FVIII, and one patient who was treated with emicizumab and factor eight inhibitor bypassing activity (FEIBA).

One patient treated with emicizumab + FEIBA reported thrombosis within 30 days of concentrate in 2018. There were no TMA events and no anaphylaxis events during the reporting period. Additionally, one patient treated with emicizumab reported an allergic and other acute reaction (rash) in 2018.

Conclusion

Of the patients with inherited bleeding disorders treated with emicizumab at centers participating in the EUHASS registry, only one reported a TE and none reported TMA or anaphylaxis events during the reporting period.

No new safety signal was suggested by the current data.

This is the first 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.

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