NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	A Post-Authorisation Safety Study to Evaluate the Safety of Marstacimab Among Patients with Haemophilia A or B using Real-World Data in Haemophilia Registers
Protocol number	B7841016
Protocol version identifier	Version 1.1
Date	20 October 2025
EU Post Authorization Study (PAS) register number	To be registered before start of data collection
Active substance	Marstacimab (PF-06741086)
Medicinal product	Hympavzi
Product reference	H0006240
Procedure number	EMEA/H/C/006240/0000
Marketing Authorization Holder(s) (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
Joint PASS	No
Research question and objective	Research question: What are the incidence rates of thromboembolic events (thrombosis) in patients with haemophilia A or B with or without inhibitors treated with marstacimab during routine clinical care in real-world settings in the United Kingdom (UK) and the United States (US)?

	The primary study objective is: • To describe the incidence rates of thromboembolic events (thrombosis) (TEs) among patients with haemophilia A or B with or without inhibitors in the patient cohort treated with marstacimab during routine clinical care. The secondary study objectives are: • To describe the incidence rates of TEs among patients with haemophilia A or B with or without inhibitors in the patient cohort unexposed to marstacimab and receiving routine prophylaxis. • To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who experience a TE. • To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who did not experience a TE.
Country(-ies) of study	United Kingdom and United States
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Marketing Authorization Holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ATHN	American Thrombosis and Hemostasis Network
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CFC	clotting factor concentrate
CRF	case report form
ED	exposure days
EDC	electronic data capture
EHL	extended half life
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EUHASS	European Haemophilia Safety Surveillance
EU	European Union
FDA	Food and Drug Administration
FIX	factor IX
FXa	factor Xa
FVIII	factor VIII
FVIIa	factor VIIa
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practice
HCP	healthcare provider

Abbreviation	Definition
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agency
HTC	haemophilia treatment center
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IgG1	immuno-globulin G1
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISPE	International Society for Pharmacoepidemiology
KM	Kaplan-Meier
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NHD	National Haemophilia Database
NHS	National Health Service
NI	non-interventional
OLE	open label extension
PASS/PAS	Post-authorisation Safety Study
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	serious adverse event
SAP	Statistical Analysis Plan
SHL	standard half-life

Abbreviation	Definition
TE	thromboembolic event (thrombosis)
TFPI	tissue factor pathway inhibitor
UBC	United BioSource LLC
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organization
US	United States
WBDR	World Bleeding Disorders Registry

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: A Post-Authorisation Safety Study to Evaluate the Safety of Marstacimab Among Patients with Haemophilia A or B using Real-World Data in Haemophilia Registers

Protocol 1.1, dated 20 October 2025

Main author: Li Wang, PhD, MBA, MS

Affiliation: Pfizer Inc.

Rationale and background

Haemophilia A and B are bleeding disorders caused by a deficiency of coagulation factor VIII (FVIII) or coagulation factor IX (FIX), respectively, each of which is a key component of the intrinsic pathway.[1] Treatment of haemophilia is primarily achieved through replacement of the missing FVIII or FIX. However, inhibitors to factor replacement products occur in up to 32% of severe haemophilia A patients[2,3,4] and in up to 5% of severe haemophilia B patients.[2,5,6,7] At high titers, inhibitors can preclude establishment of haemostatic levels of FVIII or FIX activity, contribute to increased disease-related morbidity, and historically have been associated with increased disease-related mortality. The occurrence of inhibitors imposes a substantial additional burden of disability on patients with haemophilia, and the presence of inhibitors in haemophilia A patients renders surgery a high--risk procedure.[8] In addition, effective prophylactic treatment of haemophilia B non-inhibitor patients requires intravenous injection of coagulation factor at intervals ranging from 2 times each week to once every 2 weeks,[2,9,10] which results in difficulties in adherence and reduced quality of life.[11]

Marstacimab is a human monoclonal IgG1 that targets the Kunitz 2 domain of antibody targeting the Tissue Factor Pathway Inhibitor (TFPI). TFPI is a protease inhibitor, which acts as an antagonist of the extrinsic coagulation pathway via inhibition of factor VIIa (FVIIa) and factor Xa (FXa). TFPI shuts down and inhibits a key protein in the extrinsic pathway, and thus is not expected to cause antibody immune responses against FVIII or FIX. Ex-vivo data indicates that a reduced quantity of TFPI in human plasma is associated with faster coagulation times and increased thrombin generation. In the pivotal Phase 3 study, when compared to factor replacement, marstacimab demonstrated superiority compared to on-demand treatment and non-inferiority and superiority compared to routine prophylaxis as measured by annualized bleeding rate of treated bleeds. Marstacimab was safe and well tolerated with no notable safety findings when administered as routine prophylaxis to prevent bleeding episodes in participants 12 years of age and above with haemophilia A or B with or without inhibitors with treatment of 12 months.

Marstacimab was first approved in the United States (US) on 11 October 2024 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or haemophilia B (congenital factor IX deficiency) without

factor IX inhibitors. Marstacimab was approved in the European Union (EU) on 18 November 2024 for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

Based on a review publication and clinical trials of non-replacement therapies for haemophilia targeting TFPI, thromboembolic events (thrombosis) (TEs), although rare, have been reported for these monoclonal antibodies.[12] TEs have been categorized as an important identified risk and are being assessed as adverse events of interest. To assess TEs among patients with haemophilia A or B with or without inhibitors who are treated with marstacimab in real-world settings, an active surveillance study using data from several haemophilia registers will be conducted. Using a variety of registers will provide a larger and more heterogeneous patient population for study and should enable an assessment of safety risk among patient populations (e.g., older adults) less represented in the clinical trials.

A feasibility assessment was performed to evaluate potential data sources. Based on the assessment, Pfizer determined that World Bleeding Disorders Registry (WBDR), the United Kingdom Haemophilia Centers Doctor's Organization (UKHCDO) and the American Thrombosis and Hemostasis Network (ATHN) have the infrastructure and data fields to enable collection of adequate data on clinical characteristics, comorbidities, treatment, and incidence of TEs, and therein are suitable for long-term follow-up of patients. However, when considering additional factors such as availability of data on concomitant treatments, detailed alignment of variables to the study protocol and the generalizability of the register populations, UKHCDO and ATHN are being considered as the registers to be utilized for this post-authorisation safety study (PASS).

As part of the Risk Management Plan (RMP) included in the Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA), this protocol describes a PASS to evaluate the important identified risk thromboembolic events listed in the RMP in patients with haemophilia A or B with or without inhibitors and with and without marstacimab treatment in real-world settings in the United Kingdom (UK) and the United States (US). This non-interventional study is designated as a PASS and is a post-marketing commitment to the EMA.

Research question and objective

The study will address the research question: What are the incidence rates of TEs in patients with haemophilia A or B with or without inhibitors treated with marstacimab during routine clinical care in real-world settings in the UK and the US?

The primary study objective is:

- To describe the incidence rates of TEs among patients with haemophilia A or B with or without inhibitors in the patient cohort treated with marstacimab during routine clinical care.

The secondary study objectives are:

- To describe the incidence rates of TEs among patients with haemophilia A or B with or without inhibitors in the patient cohort unexposed to marstacimab and receiving routine prophylaxis.
- To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who experience a TE.
- To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who did not experience a TE.

Study design

This is a multi-country, non-interventional, prospective cohort study to evaluate the incidence of TEs in patients with haemophilia A or B with or without inhibitors treated with marstacimab in real-world settings in the UK and the US. Data will be collected for up to 8 years from the start of the study, with a 7-year patient identification period. Patients may be included in the study at any time during this study period and will be followed until lost to follow-up in their originating register, withdrawal of consent from their originating register, death, or the end of the study, whichever comes first. Patients who are identified at the beginning of the data extraction period will be followed for a maximum of 8 years, providing no loss to follow-up, death or withdrawal.

This secondary data collection study will be conducted by using anonymized patient-level data from existing and ongoing haemophilia registers in the UK and the US. For contextualization and risk characterization purposes, cohorts unexposed to marstacimab and receiving routine prophylaxis with or without inhibitors will also be assembled from the selected registers.

Anonymized patient-level data from all participating registers will be transferred electronically into a central integrated database. Aggregate data presented in the reports will be available to regulatory agencies for review.

The study period is anticipated to start in February 2026, with data collection ending in February 2034.

Population

Two patient cohorts will be included in the study:

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who have been treated with marstacimab in a routine care setting after marstacimab has become commercially available in the UK and the US.

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who are unexposed to marstacimab and are receiving routine prophylaxis in a routine care setting.

Variables

Data to be collected in this study may include, but are not limited to, the variables listed below. Data available from each participating register will be determined based on the full feasibility assessment. The study will follow the recommendations of the EMA *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products,*[13] and *Guideline on the clinical investigation of recombinant and human plasma-derived factor IX products*[14]*,* as applicable.

A summary of the variables (where data are available) to be included is indicated below:

- Administrative information (data source)
- Patient demographic information
    - Date of birth or age at entry into the cohort, sex, race, ethnicity
- Medical history
    - Haemophilia type, date of diagnosis, severity, family history, inhibitor status
    - Other medical history (history of thromboembolic events, history of cardiovascular disease, history of hepatic events, history of autoimmune disorders, history of HIV)
    - Relevant laboratory measures and other testing
    - Concomitant medications (for each: date initiated, product, dose, frequency)
    - Co-morbidities (for each: diagnosis, date of diagnosis)
- Exposure
    - Haemophilia treatment (for each: date initiated, product, dose, frequency)
- Outcome of interest

  - Thromboembolic events including angina, deep vein thrombosis, pulmonary embolism, pulmonary infarction, arterial thromboembolic events, myocardial infarction, stroke and thrombotic microangiopathy (for each: diagnosis, date of the event)

- Risk factors for TEs (history of coronary artery disease, thrombotic microangiopathy, history of venous or arterial thrombosis or ischaemic disease, obesity, diabetes, kidney disease, and cancer)

- Safety

  - Serious adverse events

  - Vital status/mortality

Data sources

A data source feasibility assessment was performed to evaluate potential data sources. Preliminary results suggested that the haemophilia registers World Bleeding Disorders Registry (WBDR), the United Kingdom Haemophilia Centers Doctor's Organization (UKHCDO) and the American Thrombosis and Hemostasis Network (ATHN) have the infrastructure and data fields to enable collection of adequate data on clinical characteristics, comorbidities, treatment, and the incidence of TEs, and therein are suitable for long-term follow-up of patients. However, when considering additional factors such as availability of data on concomitant treatments, detailed alignment of variables to the study protocol and the generalizability of the register populations, the UKHCDO and ATHN were selected as the registers to be utilized for this PASS study.

Study size

As a descriptive non-interventional study, a sample size calculation to address hypothesis testing is not applicable. Data on all eligible marstacimab-exposed patients in each selected data source during the study period will be included. Eligible patients who have not been exposed to marstacimab will be matched to the marstacimab-exposed patients in a 1:1 ratio. As there are no pre-specified statistical hypotheses, no minimum sample size will be required. Precision estimates are provided in Table 2. Sample size will not be capped and will continue throughout the data extraction period. Based on commercial forecasts, Pfizer anticipates a minimum of 220 patients to be included in the marstacimab exposure cohort by February 2033 with data collection completed in February 2034.

Data analysis

Descriptive statistics will be presented for each cohort. For categorical variables, the frequency and percentage will be reported. For continuous variables, the number of patients with available data, mean, median, standard deviation, range, minimum, and maximum values will be presented. In addition, the number of patients with missing data will be summarized for each variable. Patients who switch between treatments during the study will contribute patient years to each cohort as applicable. Additional details will be provided in the Statistical Analysis Plan (SAP).

Patient-level data from both registers will be pooled for analysis. Crude incidence rates and associated two-sided, 95% confidence intervals (CIs) will be estimated for TEs . Crude incidence rates will be calculated as the number of enrolled patients who experience the outcome divided by the cumulative observed time at risk and presented per 1,000 patient-years at risk. Time from index date to first occurrence of the event will be calculated for TE outcomes. If possible, based on the feasibility assessment of core data elements collected in each register and the level of heterogeneity across registries, subgroup analyses of safety outcomes may be conducted.

Patients may be included in the study at any time during the study period and will be followed until lost to follow-up in their originating register, withdrawal of consent from their originating register, death, or the end of the study, whichever comes first. Data will be collected for up to 8 years from the start of the study, with a 7-year patient identification period. Patients who are identified at the beginning of the data extraction period will be followed for a maximum of 8 years, providing no loss to follow-up, death or withdrawal.

The clinical characteristics of patients (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis [e.g., prophylaxis factor replacement or bypassing agents]) who experience a TE, as well as those who did not experience such an event, will be descriptively summarized.

Details of the analyses will be provided in the SAP.

Milestones

The study protocol will be submitted to the EMA within 6 months of marstacimab approval by the European Commission. Study progress will be included in each periodic safety update report (PSUR) after the start of data collection. An interim study report will be submitted approximately 4 years after the start of data collection. The final study report will be submitted to regulatory agencies within 1 year after the end of data collection.

5. AMENDMENTS AND UPDATES

Non-applicable.

6. MILESTONES

Milestone	Planned date
Start of data collection	February 2026
End of patient identification (enrollment)	February 2033
End of data collection	February 2034
Study progress	With each PSUR after the start of data collection
Interim report	February 2030
Registration in the Heads of Medicines Agency (HMA)-European Medicines Agency (EMA) Catalogues of real-world data sources and studies	Before start of data collection
Final study report	February 2035

7. RATIONALE AND BACKGROUND

Haemophilia A and B are bleeding disorders caused by a deficiency of coagulation factor VIII (FVIII) or coagulation factor IX (FIX), respectively, each of which is a key component of the intrinsic pathway.[1] Haemophilia is an X-linked bleeding disorder with a worldwide incidence of approximately 1 of 5,000 male births.[13,14] Haemophilia B has an estimated worldwide incidence of 5 per 100,000.[15] Haemophilia A, the most common form of haemophilia, has an incidence of 24.6 per 100,000 males.[16]

Treatment of haemophilia is primarily achieved through replacement of the missing FVIII or FIX. However, inhibitors to factor replacement products occur in up to 32% of severe haemophilia A patients[2,3,4] and in up to 5% of severe haemophilia B patients.[2,5,6,7] At high titers, inhibitors can preclude establishment of haemostatic levels of FVIII or FIX activity, contribute to increased disease-related morbidity, and historically have been associated with increased disease-related mortality. The occurrence of inhibitors imposes a substantial additional burden of disability on patients with haemophilia, and the presence of inhibitors in haemophilia A patients renders surgery a high-risk procedure.[8] In addition, effective prophylactic treatment of haemophilia B non-inhibitor patients requires intravenous injection of coagulation factor at intervals ranging from 2 times each week to once every two weeks,[2,9,10] which results in difficulties in adherence and reduced quality of life.[11]

Marstacimab is a human monoclonal IgG1 that targets the Kunitz 2 domain of antibody targeting the Tissue Factor Pathway Inhibitor (TFPI). TFPI is a protease inhibitor, which acts as an antagonist of the extrinsic coagulation pathway via inhibition of factor VIIa (FVIIa) and factor Xa (FXa). TFPI shuts down and inhibits a key protein in the extrinsic pathway, and thus is not expected to cause antibody immune responses against FVIII or FIX. Ex-vivo data indicates that a reduced quantity of TFPI in human plasma is associated with faster coagulation times and increased thrombin generation. In the pivotal Phase 3 study, when compared to factor replacement, marstacimab demonstrated superiority compared to on-demand treatment and non-inferiority and superiority compared to routine prophylaxis as measured by annualized bleeding rate of treated bleeds. Marstacimab was safe and well tolerated with no notable safety findings when administered as routine prophylaxis to prevent bleeding episodes in participants 12 years of age and above with haemophilia A or B without inhibitors with treatment of 12 months.

Marstacimab was approved first in the US on 11 October 2024 for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with haemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or haemophilia B (congenital factor IX deficiency) without factor IX inhibitors. Marstacimab was approved in the EU on 18 November 2024 for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

Based on a review publication and clinical trials of non-replacement therapies for haemophilia targeting TFPI, TEs, although rare, have been reported for these monoclonal antibodies.[12] TEs have been categorized as an important identified risk and are being assessed as adverse events of interest. To assess the important identified risk of this primary safety event of interest among patients with haemophilia A or B with or without inhibitors who are treated with marstacimab in the real-world in the UK and the US, an active surveillance study using data from several haemophilia registers is proposed. Using a variety of registers will provide a larger and more heterogeneous patient population for study and should include data on the identified safety risks among patient populations less represented in the clinical trials, such as older adults.

As part of the Risk Management Plan (RMP) included in the Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA), this protocol describes a post-authorisation safety study (PASS) to evaluate the incidence of TEs in patients with haemophilia A or B with or without inhibitors and with and without marstacimab treatment in real-world settings in the UK and the US. This non-interventional study is designated as a PASS and is a post-marketing commitment to the European Medicines Agency (EMA).

8. RESEARCH QUESTION AND OBJECTIVES

Research Question:

The study will address the research question: What are the incidence rates of TEs in patients with haemophilia A or B with or without inhibitors treated with marstacimab during routine clinical care in real-world settings in the UK and the US?

Primary Objective

The primary study objective is:

- To describe the incidence rates of TEs among patients with haemophilia A or B with or without inhibitors in the patient cohort treated with marstacimab during routine clinical care.

Secondary Objectives

The secondary study objectives are:

- To describe the incidence rates of TEs among patients with haemophilia A or B with or without inhibitors in the patient cohort unexposed to marstacimab and receiving routine prophylaxis.

- To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who experience a TE.

- To describe clinical characteristics of patients with haemophilia A or B with or without inhibitors (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who did not experience a TE.

9. RESEARCH METHOD

9.1. STUDY DESIGN

This is a multi-country, non-interventional, prospective cohort study to evaluate the incidence of TEs in patients with haemophilia A or B with or without inhibitors treated with marstacimab in real-world settings in the UK and the US. Data will be collected for up to 8 years from the start of the study, with a 7-year patient identification period. Both patients exposed to marstacimab and those unexposed who meet the eligibility criteria may be included in the study at any time during this study period and will be followed until lost to follow-up in their originating register, withdrawal of consent from their originating register, death, or the end of the study, whichever comes first. Patients who are enrolled at the beginning of the data extraction period will be followed for a maximum of 8 years, providing no loss to follow-up, death or withdrawal.

The strength of this study is the cumulative population generated by combining data from different national registers. Each register will provide information on consecutive eligible patients who represent a broad range of evolving clinical practices and outcomes across countries and health care systems. These registers typically have more complete data on clinical characteristics and treatment history and include longer-term follow-up compared to data available in clinical trials. In addition, this study should be representative of treated patient populations in the UK and the US. Therefore, this study will provide a comprehensive characterization of the incidence of TEs in patients with haemophilia A or B with or without inhibitors treated with marstacimab and in those receiving contemporary and evolving treatments.

Patient registers may provide a characterization of the indicated population according to co-morbidities, medication use, complications and adverse events, data on disease epidemiology in terms of prevalence, incidence and natural outcomes, and a measure of the baseline risks associated with standards of care. In addition, patient registers may allow the capture of unexposed patients with similar demographic and clinical characteristics to the exposure cohort under study (e.g., disease severity, age group, median/mean follow-up time, comorbidities) for contextualization.

This secondary data collection study will be conducted by using anonymized patient-level data from existing and ongoing haemophilia registers in the UK and the US. For contextualization and risk characterization purposes, cohorts unexposed to marstacimab and receiving routine prophylaxis will also be assembled from the selected registers.

Anonymized patient-level data from both participating registers will be transferred electronically into a central integrated database. Aggregate data presented will be available to regulatory agencies for review.

9.2. Setting

Two patient cohorts will be included in the study:

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who have been treated with marstacimab in a routine care setting after marstacimab has become commercially available in the UK and the US.

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who are unexposed to marstacimab and are receiving routine prophylaxis in a routine care setting.

Patients in the unexposed cohort will be matched within their originating register in a 1:1 ratio to the marstacimab exposure cohort by age group, index date, haemophilia severity, inhibitor status, history of TE, and history of cardiovascular disease.

Data will be collected for up to 8 years from the start of the study, with a 7-year patient identification period. Patients in both cohorts who meet the eligibility criteria may be

included in the study at any time during this study period and will be followed until lost to follow-up in their originating register, withdrawal of consent from their originating register, death, or the end of the study, whichever comes first. Patients who are identified at the beginning of the study period will be followed for a maximum of 8 years, providing no loss to follow-up, death or withdrawal.

9.2.1. Inclusion Criteria

The study inclusion criteria are specific for each cohort, as indicated below. The inclusion and exclusion criteria are subject to amendments, and final criteria will be based on the approved local labels. These eligibility criteria are intended to make the two cohorts as similar as possible.

Patients must meet all the following inclusion criteria specific to the applicable cohort to be eligible for inclusion in the study.

Marstacimab Exposure Cohort

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who have been treated with commercial marstacimab in a routine care setting in the UK or the US.

Unexposed Cohort

- Patients 12 years of age and older with haemophilia A or B with or without inhibitors who have not been treated with marstacimab and are receiving routine prophylaxis in a routine care setting in the UK or the US.

*Note: Patients in the unexposed cohort who initiate commercial marstacimab during the follow-up period will be switched to the marstacimab exposure cohort. Their exposure time will be counted as applicable in each cohort.

9.2.2. Exclusion criteria

There are no exclusion criteria.

9.2.3. Risk Window

There will be no wash out period between treatments. Each patient's marstacimab exposure begins as of the index date (i.e., the date of first administration of commercial marstacimab after study start on or after 11 October 2024, the date of marstacimab approval in the US). The date of marstacimab discontinuation is not available in the UKHCDO and ATHN registers; therefore, the treatment end date or treatment discontinuation will be initiation of a non-marstacimab routine prophylaxis treatment.

A non-marstacimab exposure episode begins as of the index date (i.e., date study eligibility criteria are met and/or an EMA-approved routine prophylaxis treatment is initiated). All time following the start of the risk period is included up to the censoring date, irrespective of non-

marstacimab exposure during this time. Exposure to different non-marstacimab treatments may occur and there may be periods of no medication use. If a patient switches to marstacimab, they will be censored for the non-marstacimab cohort and enrolled into the marstacimab cohort.

Additional details on risk windows and switching will be described in the SAP.

9.3. Variables

Table 1 describes the core data fields to be captured in this study. Pfizer will aim to collect all variables listed in Table 1 for both the exposed and unexposed cohorts. However, as this study relies on secondary data collection from existing haemophilia registers, these variables may need to be readjusted for one or both cohorts based on the data that it will ultimately be feasible to collect from the registers' respective databases as these databases continue to evolve. Operational definitions will be provided in the SAP.

The data to be captured will document normal clinical practice, and no specific investigations outside of normal clinical practice will be requested.

Table 1. Variables, their roles, and data source(s)

Variable*	Role	Data source(s)*
Demographic and Diagnostic Data		
Registry Source Identifier	Demographic	Site
Month and year of birth	Demographic Baseline characteristic	UKHCDO/ATHN
Sex	Demographic Baseline characteristic	UKHCDO/ATHN
Race and Ethnicity	Demographic Baseline characteristic	UKHCDO/ATHN
Weight	Demographic Baseline characteristic	UKHCDO/ATHN
Country of residence	Demographic Baseline characteristic	UKHCDO/ATHN
Pre-existing/current comorbidities	Baseline characteristics Potential confounder	UKHCDO/ATHN
History of thromboembolic events (3 years before index date)	Baseline characteristics Potential confounder	UKHCDO/ATHN
History of cardiovascular disease (3 years before index date)	Baseline characteristics Potential confounder	UKHCDO/ATHN
History of auto-immune disorders	Baseline characteristics	UKHCDO

Table 1. Variables, their roles, and data source(s)

Variable*	Role	Data source(s)*
	Potential confounder	
History of hepatitis C	Baseline characteristics Potential confounder	UKHCDO/ATHN
History of hepatitis B	Baseline characteristics Potential confounder	UKHCDO/ATHN
History of Human Immunodeficiency Virus (HIV)	Baseline characteristics Potential confounder	UKHCDO/ATHN
Concomitant medications, including steroids and immunosuppressants at cohort entry	Potential confounder	UKHCDO/ATHN
Type of haemophilia (A or B)		UKHCDO/ATHN
Haemophilia disease characteristics (mild, moderate, severe)	Baseline characteristics	UKHCDO/ATHN
Date of Diagnosis	Baseline characteristics	UKHCDO/ATHN
Baseline factor level	Baseline characteristics	UKHCDO/ATHN
Haemophilia treatments (Plasma clotting factor concentrate (CFC), recombinant standard half-life (SHL), recombinant extended half-life (EHL), non-factor replacement and other) Last treatment regimen before marstacimab	Baseline characteristics Exposure	UKHCDO/ATHN* *ATHN only collects Medication Name/Dose Start and End dates for haemophilia treatments, and only name of CFC, SHL, and EHL treatments
Risk factors for thromboembolic events (e.g., obesity, diabetes, kidney disease, cancer)	Baseline characteristics Potential confounder	UKHCDO/ATHN
Patient History of Inhibitor	Baseline characteristics Potential confounder	UKHCDO/ATHN
Treatment Exposure		UKHCDO/ATHN
Marstacimab Treatment (doses/frequency)	Main Exposure (Exposed cohort)	UKHCDO/ATHN
Date Treatment Initiated (month, year)		UKHCDO/ATHN
Other Treatment	Main exposure (Non-marstacimab cohort)	UKHCDO/ATHN
Date Treatment Initiated (month, year)		UKHCDO/ATHN
Exogenous Replacement Therapy	Other exposure	UKHCDO/ATHN
Product Administered		UKHCDO/ATHN
Concomitant Therapy, including steroids and immunosuppressants	Other exposure Potential confounder	UKHCDO/ATHN
Concomitant Coagulation Factors or By-Passing Agents, non-coagulation factor replacement	Other exposure Potential confounder	UKHCDO/ATHN

Table 1. Variables, their roles, and data source(s)

Variable*	Role	Data source(s)*
Any other concomitant medications	Other exposure Potential confounder	UKHCDO/ATHN
Safety endpoints		UKHCDO/ATHN
New diagnoses of selected medical conditions	Primary outcome	UKHCDO/ATHN
TEs (deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke, angina, thrombotic microangiopathy, pulmonary infarction))	Primary outcome	UKHCDO/ATHN
All Serious Adverse Events	Other outcome	UKHCDO/ATHN**
All-Cause Mortality, including cause and date of death when available - Intracranial haemorrhage, Bleeding (excluding intracranial) - Thromboembolic event - Liver disease, specify - Cancer, specify - Cardiac - Infection, including pneumonia - HIV - Other, specify.	Other outcome	UKHCDO/ATHN

*. The list of variables may be readjusted based on data availability from the registers. Some of these variables may not be available for the marstacimab-unexposed cohort.
**. ATHN does not capture stand-alone SAE, but if AE has association with hospitalization or death

9.4. Data sources

A preliminary data source feasibility assessment was performed to evaluate three types of potential data sources: the European Haemophilia Safety Surveillance (EUHASS); national registers that link prescription data, claims data, and data from electronic health records; and existing and ongoing haemophilia registers such as the Swedish Health Registers, the Danish Health Registers, and the SIGMA Consortium.

Criteria that were evaluated for selection of participating registers include:[18]

- Collection of the same data fields as the core data set
- Harmonization and standardization of terminology, particularly for adverse events (AEs) [Medical Dictionary for Regulatory Activities (MedDRA)]
- Patient consent for secondary uses of their data outside of the existing registry
- Strict data quality management practices and high-quality data
- Avoidance of duplication of patients with haemophilia across registers

Next, a comprehensive feasibility assessment was completed and Pfizer determined that the World Bleeding Disorders Registry (WBDR), the United Kingdom Haemophilia Centers Doctor's Organization (UKHCDO), and the American Thrombosis and Hemostasis Network

(ATHN) have the infrastructure and data fields to enable collection of adequate data on clinical characteristics, comorbidities, treatment, and incidence of TEs , and are suitable for long-term follow-up of patients. However, when considering additional factors such as availability of data on concomitant treatments, detailed alignment of variables to the study protocol and the generalizability of the register populations, the UKHCDO and ATHN are being considered as the registers to be utilized for this PASS. A description of the 2 selected registers is provided below.

The UK National Haemophilia Database (NHD), started in 1968, is a register of patients in the UK that captures clinical data on individuals diagnosed with haemophilia or other inherited bleeding disorders. Its purpose is to improve the care of people with bleeding disorders. The database is held within the National Health Service (NHS) and managed by the UKHCDO. Data from the UKHCDO will be electronically transferred directly to the central integrated database. The database currently includes data on more than 11,000 patients across England, Scotland, Wales, and Northern Ireland.

Data are entered by healthcare providers at participating treatment centers. Each patient record includes a baseline data collection at enrollment, comprising diagnosis, treatment history, and relevant medical history. Follow-up data are subsequently entered either on an ad hoc basis or in alignment with standard-of-care practices. Follow-up data elements include current treatment regimens, laboratory results, thrombotic or thromboembolic events, joint health assessments, inhibitor status, adverse events, and mortality data including cause of death.

The UKHCDO database complies with 21 CFR Part 11 and/or EudraLex Annex 11 requirements for electronic records and systems. Data integrity is maintained through automated real-time edit checks, discrepancy management processes, and manual data reviews, including data listings and programmed outputs. Patient-level data will be provided to the integrated study database.

The American Thrombosis and Hemostasis Network (ATHN) has been collecting longitudinal clinical data for over 15 years from patients with bleeding and clotting disorders. Its primary objective is to determine the safety of therapies used in the treatment of participants with congenital or acquired non-neoplastic blood disorders and connective tissue disorders with bleeding tendency. Data collection is conducted through a network of affiliated haemophilia treatment centers (HTCs) across the United States, with over 20,000 patients currently represented in the database. Participation by HTCs is voluntary.

Data capture includes a baseline assessment at the time of enrolment, which documents the patient’s diagnosis, treatment history, and relevant medical background. Follow-up data are entered in an ad hoc manner or per routine clinical care, and include information on ongoing treatments, laboratory results, thrombotic or thromboembolic events, joint health, inhibitor development, other adverse events, and death including cause. In certain contexts, data entry may also occur on an annual or biannual basis to support specific research or surveillance initiatives.

The ATHN database is compliant with 21 CFR Part 11 and/or EudraLex Annex 11 standards. Quality assurance processes include real-time data validation, discrepancy resolution workflows, and manual data review via listings and pre-specified data outputs. The ATHN will contribute patient-level data directly to the integrated study database.

Pfizer will engage in a Data Sharing Agreement or other agreement with each data source vendor. The Data Sharing Agreement will define, at a minimum, whether patient level or aggregate level data will be shared, and the eligibility criteria for patients to be transferred. The central integrated database will be used to consolidate de-identified individual patient-level data from these registers. All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Each participating register will assign a persistent and unique identifier or 'token' to each patient using a sophisticated matching algorithm. This technology enables reconciliation of duplicates, integration of data from multiple registers, and linkage of data across different datasets in a privacy compliant manner without the need to share personal identifiable information between parties.

9.5. Study Size

As a descriptive non-interventional (NI) study, a sample size calculation to address hypothesis testing is not applicable. Data on all eligible marstacimab-exposed patients in each selected data source during the study period will be included. Eligible patients who have not been exposed to marstacimab will be matched to the marstacimab-exposed patients in a 1:1 ratio. As there are no pre-specified statistical hypotheses, no minimum sample size will be required. Enrolment will not be capped and will continue throughout the study period.

Table 2 denotes the precision calculations based on different expected incidence proportions. ATHN and UKHCDO are national comprehensive registers, estimating a 95-100% inclusion rate of patients with haemophilia A and B. ATHN and UKHCDO indicate the largest non-gene therapy treated haemophilia A and B populations, exceeding 20,000 and 11,800 respectively. Based on commercial forecasts, the Sponsor anticipates a minimum of 220 patients to be included in the marstacimab exposure cohort by 2033.

The precision calculations generated in Table 2 were performed for three different sample size scenarios (n=150, n=220, n=300) and for expected incidence proportions for thromboembolic events ranging between 0.1% and 6.0%. The two-sided 95% exact binomial CIs for the observed incidence proportions were calculated using the Clopper-Pearson method. For the estimated sample size of n=220, the observed incidence proportion has a range of 0.0% (95% CI [0.0%, 1.7%]) to 5.9% (95% CI [3.2%, 9.9%]) with the given parameters. Based on the precision estimates below, the proposed/estimated sample size will suffice to adequately inform the study objectives and thus no circumventive measures are being proposed.

Table 2. Precision Calculations for Different Incidence Proportions

Number of Patients	Expected Incidence Proportion (%)	Expected Number of Patients with Event*	Observed Incidence Proportion (%)	Precision of Observed Incidence Proportion (95% CI Width#) (%)	95% CI of Observed Incidence Proportion (%)#
150	0.1	0	0.0	2.4	(0.0, 2.4)
	0.5	0	0.0	2.4	(0.0, 2.4)
	1.0	1	0.7	3.6	(0.0, 3.7)
	2.0	3	2.0	5.3	(0.4, 5.7)
	3.0	4	2.7	6.0	(0.7, 6.7)
	4.0	6	4.0	7.0	(1.5, 8.5)
	5.0	7	4.7	7.5	(1.9, 9.4)
	6.0	9	6.0	8.3	(2.8, 11.1)
220	0.1	0	0.0	1.7	(0.0, 1.7)
	0.5	1	0.5	2.5	(0.0, 2.5)
	1.0	2	0.9	3.1	(0.1, 3.2)
	2.0	4	1.8	4.1	(0.5, 4.6)
	3.0	6	2.7	4.8	(1.0, 5.8)
	4.0	8	3.6	5.5	(1.6, 7.0)
	5.0	11	5.0	6.2	(2.5, 8.8)
	6.0	13	5.9	6.7	(3.2, 9.9)

Table 2. Precision Calculations for Different Incidence Proportions

300	0.1	0	0.0	1.2	(0.0, 1.2)
	0.5	1	0.3	1.8	(0.0, 1.8)
	1.0	3	1.0	2.7	(0.2, 2.9)
	2.0	6	2.0	3.6	(0.7, 4.3)
	3.0	9	3.0	4.2	(1.4, 5.6)
	4.0	12	4.0	4.8	(2.1, 6.9)
	5.0	15	5.0	5.3	(2.8, 8.1)
	6.0	18	6.0	5.7	(3.6, 9.3)

*: Rounded down to the nearest whole number.
#: Assuming a two-sided 95% exact binomial CI based on the Clopper-Pearson method.

9.6. Data management

9.6.1. Data integrity

Pfizer will ensure that existing registers meet required register data standards including data verification. In case the required register data standards are not being met, the registers may be required to modify their data standards to be included in a central integrated database. If medical coding is required, this will be conducted by qualified personnel at United BioSource, LLC (UBC), the contract research organization conducting the study.

9.6.2. On-going data extraction from existing registers

Relevant data will be extracted from the selected registers every 6 months, at a minimum, for 8 years. Anonymized patient-level data from all participating registers will be transferred electronically into a central integrated database. Aggregate data presented in the reports will be available to regulatory agencies for review.

All electronic data received from the participating registers are the property of each register. UBC will apply data integrity checks and provide output to each register that will be responsible for review of discrepancies and actioning as appropriate according to each register's data cleanliness guidelines.

Data for patients who wish to no longer participate in their originating register (assent and/or consent withdrawn) will only be maintained up to the time that they withdrew consent from the originating register. Any data after the withdrawal of consent will not be uploaded into the integrated study database.

9.7. Data analysis

Detailed methodology for summaries and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

This is a descriptive study with a focus on estimation and not hypothesis testing.

Descriptive statistics will be presented for each cohort. For categorical variables, the frequency and percentage will be reported. For continuous variables, the number of patients with available data, mean, median, standard deviation, range, minimum, and maximum values will be reported. In addition, the number of patients with missing data will be summarized for each variable. No imputation of missing values will be performed, except in the case of partial dates which will be outlined in the SAP. Patients who switch between treatments during the study will contribute patient years to each cohort as applicable. Additional details will be provided in the SAP.

Patient-level data from both registers will be pooled, and analysis will be conducted by cohort.

Crude incidence rates and incidence proportions, and associated two-sided 95% CIs, will be estimated for TEs. Crude incidence rates will be calculated as the number of enrolled patients who experience the outcome divided by the cumulative observed time at risk and presented per 1,000 patient-years at risk. Incidence proportions will be calculated as the number of enrolled patients who experience the outcome divided by the number of patients at risk.

Time from index date to first occurrence of the event will be calculated for TE outcomes descriptively. Patients will be followed until lost to follow-up in their originating register, withdrawal of consent from their originating register, death, or the end of the study, whichever comes first Patients not experiencing the outcome will be censored at the last date they were known to be outcome-free. Censoring rules will be provided in the SAP.

Subgroup analyses of outcomes may be conducted if sample size permits, based on the feasibility assessment of core data elements collected in each register and the level of heterogeneity across the registers. These subgroup analyses may include, but are not limited to, inhibitor status, history of cardiovascular disease in the 3 years prior to the index date, and history of TEs in the 3 years prior to the index date. These subgroup analyses are intended for descriptive purposes only, and, therefore, no statistical hypothesis testing will be performed.

The clinical characteristics of patients (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who experience a TE will be descriptively summarized. In addition, the clinical characteristics of patients (those exposed to marstacimab and those unexposed to marstacimab and receiving routine prophylaxis) who did not experience a TE will be summarized.

Note: Patients in the unexposed cohort who initiate commercial marstacimab during the follow-up period will be switched to the marstacimab exposure cohort. Their exposure time will be counted as applicable in each cohort.

9.8. Quality control

The below describes the basis on which registers were selected for inclusion in this study. Pfizer will conduct oversight of these registers to ensure the requirements remain valid throughout the course of the study.

The registers providing data for this study were selected based on their geographic coverage, data collection methodology, completeness of the variables collected, and processes for data cleaning and quality checks. Data captured may include both prospective and retrospective data.

- Specifically, the registers selected for this study met the following minimum quality criteria: established processes for data cleaning and quality checks; approval from relevant oversight bodies (e.g., ethical committees), if applicable.

- Pfizer/UBC will ensure that existing registers meet required register data standards including data verification.

9.9. Limitations of the research methods

Given that this study will provide information on the clinical management of patients with haemophilia A and haemophilia B with or without inhibitors across multiple countries, there is a potential limitation due to variations in the standard of care across countries or regions and variations in treatments due to cultural norms resulting in the potential for missing data for some measures and possible lack of generalizability. Missing data may bias the analyses if some data elements are only available in specific subgroups of patients. This has been noted as a potential issue for all rare disease registries.

Another limitation is that treatment patterns for haemophilia will evolve over the long duration of this study with the introduction of new therapies, treatment recommendations, and approaches to patient management. The rates of events of interest and their distribution among patient types may change over time.

Further, the reference population in this study may not be exclusively contemporaneous to marstacimab treated patients. The potential lack of a comparable reference population and lack of randomization which are known limitations inherent to these types of registers make this register vulnerable for confounding. Also, analyses may be unable to identify or control for any changes in rates due to changes in the treatment landscape.

Although every effort will be made to collect all variables as listed in Table 1 to fulfill the study objectives, this study is based on anonymized secondary data collection from registers; therefore, the variables that can be collected will ultimately be dictated by those collected in the registers' respective databases.

Another limitation of this study is that given that haemophilia is a rare disease and the populations under study may be small, particularly for the patients with haemophilia B, the precision with which the incidence of TE can be estimated will be limited.

The unexposed cohort is included for contextualization. There may be two potential sources of bias related to the cohort unexposed to marstacimab: (1) not using a new user design and (2) having an active unexposed cohort without specifying their treatment. Since marstacimab will be new to the market at the beginning of data collection in each register, patients will likely be new users, i.e., an inception cohort. The eligibility criteria for the unexposed cohort does not reflect a new user design. The unexposed cohort will be prevalent users of routine prophylaxis. Selecting one active non-marstacimab treatment may result in small numbers of patients actively being treated with any one specific treatment. Even broadening the criteria to treatment initiation with one of several specified treatments may result in slow enrollment, or patient identification might have to begin earlier than the identification of the marstacimab cohort in order to identify the treatment initiation date.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in:

- Agency for Healthcare Research and Quality: Registries for Evaluating Patient Outcomes: A User's Guide [Internet][17]

- EMA Patient Registries Workshop, 28 October 2016[18]
- EMA Guideline on registry-based studies[19]
- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee[20]
- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[21]
- Good practices for Real-World data studies of treatment and/or comparative effectiveness: Recommendations from the joint International Society for Pharmacoeconomics and Outcomes Research/International Society for Pharmacoepidemiology (ISPOR-ISPE) Special Task Force on Real-World Evidence in Health Care Decision Making[22]
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)[23]
- EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology[24]
- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies[25]
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment[26]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be registered publicly in the Heads of Medicines Agency (HMA)/ EMA catalogue of real-world data studies (https://catalogues.ema.europa.eu/).

Anonymized patient-level data from all participating registries will be transferred electronically into the integrated study database. Aggregate data presented in the reports will be available to regulatory agencies for review

After the start of data collection, study progress will be included in the periodic safety update reports (PSURs). An interim study report will be submitted 4 years after the start of data collection. The final study report will be submitted to regulatory agencies within 1 year after the end of data collection, anticipated February 2035.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Sponsor product, Pfizer should be informed immediately.

13. REFERENCES

1. Zimmerman B, Valentino LA. Hemophilia: in review. Pediatr Rev 2013;34:289-94

2. Berntorp E, Shapiro AD. Modern haemophilia care. Lancet. 2012;379(9824):1447-56

3. Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013; 368(3):231-9

4. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: A systematic review. Haemophilia 2003;9(4):418-35

5. Srivastava A, Santagostino E, Dougall A, et al. World Federation of Hemophilia. WFH Guidelines for the Management of Hemophilia, 3rd edition. Haemophilia. 2020;26(Suppl 6):1-58

6. Sultan Y. Prevalence of inhibitors in a population of 3435 hemophilia patients in France. French Hemophilia Study Group. Thrombosis and Haemostasis. 1992;67(6):600-2

7. Shapiro AD, Di Paola J, Cohen A, et al. The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B. Blood. 2005;105(2):518-25

8. Hay CRM, Brown S, Collins PW, et al. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. Br J Haematol. 2006;133(6):591-605

9. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX Fc fusion protein in hemophilia B. N Engl J Med. 2013;369(24):2313-23

10. BeneFIX SmPC. Last updated 22 September 2021. Combo of decision and SmPC: https://gdms.pfizer.com/gdms/drl/objectId/090177e19cd4fccb

11. Lillicrap D. Extending half-life in coagulation factors: where do we stand? Thrombosis Research. 2008; 122 (Suppl. 4):S2–S8

12. Gualtierotti R, Pasca S, Ciavarella A, Arcudi S, Giachi A, Garagiola I, Suffritti C, Siboni SM, Peyvandi F. Updates on Novel Non-Replacement Drugs for Hemophilia. Pharmaceuticals (Basel). 2022 Sep 23;15(10):1183.

13. European Medicines Agency. Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. July 26, 2018. Accessed July 7, 2023.

14. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404-413.

15. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf

16. Nathwani, AC, Nienhuis, AW, Davidoff, AM. (2014). Our journey to successful gene therapy for hemophilia B. Hum. Gene Ther. 25, 923–926

17. Nienhuis, AW, Nathwani, AC, and Davidoff, AM. (2016). Gene therapy for hemophilia. Hum. Gene Ther. 27, 305–308

18. World Federation of Hemophilia. Report on the Annual Global Survey 2020. October 2021. Accessed August 24, 2022. https://www1.wfh.org/publications/files/pdf-2045.pdf

19. Darby, SC, Kan, S.W., Spooner, RJ, Giangrande, PL, Hill, FG, Hay, CR, Lee, CA, Ludlam, CA, and Williams, M. (2007). Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood 110, 815–825

20. Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr [cited 2019 15 Jun]. Available from http://www.ncbi.nlm.nih.gov/books/NBK208616/

21. European Medicines Agency. Guideline on registry-based studies. October 22, 2021. Accessed 1 May 2024. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf

22. EMA Patient Registries Workshop, 28 October 2016 https://www.ema.europa.eu/en/documents/report/report-patient-registries-workshop_en.pdf

23. Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2016; 25:2-10

24. Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp

25. Good practices for Real-World data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on Real-World evidence in health care decision making https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372

26. International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS). https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies

27. European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

28. The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studieshttp://www.encepp.eu/code_of_conduct/

29. Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessmenthttps://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ ucm071696.pdf/

14. LIST OF TABLES

15. LIST OF FIGURES

None

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

NUMBER	DOCUMENT REFERENCE NUMBER	DATE	TITLE
1	1	5/14/24	PFIZER MARSTACIMAB REGISTRY QUESTIONNAIRE V2

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: A Post-Authorisation Safety Study to Evaluate the Safety of Marstacimab Among Patients with Severe Haemophilia A or B using Real-World Data in European Haemophilia Registers

EU PAS Register® number: Study not yet registered.
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the Europe PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Study not yet registered in Europe PAS Register, will register before start of data collection.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.
2.1.2 The objective(s) of the study?	☒	☐	☐	8.
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[From section 9.7] This is primarily a descriptive study with focus on estimation and not hypothesis testing. Descriptive statistics will be presented.

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.4
	4.2.2 Age and sex	☒	☐	☐	9.3
	4.2.3 Country of origin	☒	☐	☐	9.4
	4.2.4 Disease/indication	☒	☐	☐	9.4
	4.2.5 Duration of follow-up	☒	☐	☐	9.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

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Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	
	9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7
10.4	Are stratified analyses included?	☐	☒	☐	
10.5	Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

As a descriptive non-interventional study, a sample size calculation is not applicable. Detailed statistical methodology will be described in the Statistical Analysis Plan

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.7.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐		5.

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Li Wang

Date: 2 May 2025

Signature:

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

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