HYMPAVZI (MARSTACIMAB) RISK MANAGEMENT PLAN

RMP Version number: 2.2

Data lock points for this RMP:

- 29 April 2025 for study protocol B7841005
- 30 May 2025 for study protocol B7841007
- 26 May 2025 for study protocol B7841008

Date of final sign off: 19 February 2026

Rationale for submitting an updated RMP: RMP is being submitted to to align the information in the EU-RMP with the updated information in the marstacimab SmPC.

Summary of significant changes in this RMP:

- PART II, Module SVII.3 was updated: Updated to align with changes in the marstacimab SmPC
- PART V, Section V.1 was updated: Updated to align with changes in the marstacimab SmPC
- PART VI, Section II.B was updated to accurately reflect the RMP summary taking in account the updates listed above
- Modifications to Annex 8

Other RMP versions under evaluation: None

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
aPCC	Activated Prothrombin Complex Concentrate
aRMM	Additional Risk Minimization Measures
ATC	Anatomical Therapeutic Chemical
AVDOS	Average Daily Dose
BBIs	Blood Borne Infections
CD4	Cluster of Differentiation 4
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
COVID-19	Coronavirus Disease-2019
CrCl	Chromium Chloride
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
EEA	European Economic Area
eGFR	Estimated Glomerular Filtration Rate
EHL	Extended Half-Life
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EURD	European Union Reference Date
FDA	Food and Drug Administration
FIX	Factor IX
FVIII	Factor VIII
FXa	Factor Xa
GVP	Good Pharmacovigilance Practices
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	High Level Term
IBD	International Birth Date
ICH	Intracranial Haemorrhage
IgG1	Immunoglobulin G Subclass 1
IVIG	Intravenous Immunoglobulin
LLN	Lower Limit of Normal
INN	International Nonproprietary Name
ISR	Injection Site Reaction
ITI	Immune Tolerance Induction
IU	International Unit

IV	Intravenous
IVIG	Intravenous Immunoglobulin
K2	Kunitz domain 2
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
NO	Nitric Oxide
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OLE	Open Label Extension
PASS	Post-Authorisation Safety Studies
PCC	Prothrombin Complex Concentrates
PK	Pharmacokinetic
PL	Patient Leaflet
PSUR	Periodic Safety Update Report
PT	Preferred Term
QW	Every week
RMP	Risk Management Plan
SC	Subcutaneous
SD	Standard Deviation
SHL	Standard Half-Life
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SoC	Standard of Care
SU	Standard Unit
TFPI	Tissue Factor Pathway Inhibitor
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USPI	United States Package Insert

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Marstacimab
Pharmacotherapeutic group(s) (ATC Code)	Antihemorrhagics, other systemic haemostatics, ATC code: B02BX11
Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Hympavzi
Marketing authorisation procedure	Centralized
Brief description of the product:	Chemical class: Marstacimab is a human monoclonal antibody (mAb) of the G isotype, subclass 1 (IgG1).
	Summary of mode of action: Marstacimab is a human monoclonal antibody (mAb) of the G isotype, subclass 1 (IgG1) that targets the functional Kunitz domain 2 (K2) of Tissue Factor Pathway Inhibitor (TFPI), the primary inhibitor of the extrinsic coagulation cascade.
	Important information about its composition: Marstacimab is an IgG1 human mAb with two heavy (H) chains and two light (L) chains, covalently linked with four inter-chain disulfide bonds. PF 06741086 is capable of binding TFPI at the Kunitz 2 domain in a dose dependent manner thus preventing formation of the TFPI:FXa complex and therefore resulting in free FXa
Hyperlink to the Product Information:	Module 1.3.1 (Proposed Product Information)
Indication(s) in the EEA	Current: 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 FVIII inhibitors; or Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia B (congenital factor IX deficiency, FIX <1%) without FIX inhibitors.

	Proposed: Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:
	
	• Haemophilia A (congenital factor VIII deficiency):
	  ○ Without factor VIII inhibitors who have severe disease (FVIII < 1%)
	  ○ With factor VIII inhibitors

	• Haemophilia B (congenital factor IX deficiency): o Without factor IX inhibitors who have severe disease (FIX < 1%) o With factor IX inhibitors
Dosage in the EEA	Current: Solution for Injection at a concentration of 150 mg/mL (prefilled syringe or prefilled pen). The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by subcutaneous injection followed thereafter by 150 mg by subcutaneous injection once weekly, at any time of day.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Two presentations of marstacimab Solution for Injection are available as: Marstacimab Solution for Injection at a concentration of 150 mg/mL is provided in a prefilled syringe and stoppered with a grey coated plunger stopper (nominal fill volume of 1 mL). Marstacimab Solution for Injection at a concentration of 150 mg/mL is provided in a single-use, disposable prefilled pen intended for SC administration by the user. The prefilled pen contains the 1 mL prefilled syringe described above
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years 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.

Congenital haemophilia A and haemophilia B are X-linked recessive disorders affecting almost exclusively males.[1] The disorder is caused by deficiency or absence of the coagulation proteins, factor VIII (FVIII) for haemophilia A and factor IX (FIX) for haemophilia B (Berntorp et al., 2021). The classification of severity is based on the level of residual FVIII or FIX activity, where severe haemophilia is defined as levels <1% of normal, or <1 international unit (IU)/dL.[2]

Haemophilia A and haemophilia B were historically thought to be the same disease but are now recognized as separate entities[3]. Distinctions between haemophilia A and haemophilia B are made when available, but as many sources discussed both disorders, some important information was only found for overall haemophilia (A and B). Thus, each section is presented with an overview on overall haemophilia, followed by separate subsections with specific information for haemophilia A, and haemophilia B.

Due to haemophilia being a congenital and sex-linked disorder, the literature base and this report, by proxy, is primarily focused on reporting outcomes related to biologic males. Outcomes related to biologic females were not widely described in the literature and are included when applicable. Age is rarely reported in the literature on haemophilia, and wherever age is not specifically indicated in this text, the total population should be assumed.

To identify relevant information relating to the epidemiology of haemophilia in the EU, a search in PubMed was conducted using the term haemophilia/hemophilia in combination with the 27 countries included in EU. The search was limited to publications in English, with an abstract, studies done in humans, and published between January 2018 and February 2023. Important and relevant references cited within reviewed articles were also obtained. Furthermore, websites of identified European haemophilia registries were searched for additional publications or reports.

Incidence:

As haemophilia A and B are congenital, nontransmissible disorders, new “incident” cases do not arise in the population over time. Instead, birth prevalence, which is calculated as the number of cases in relation to number of births, is a more meaningful estimation of “incidence”. For haemophilia, more specifically, the number of male births is the usual denominator used when evaluating birth prevalence.

Prevalence:

The reported haemophilia prevalence varied significantly across European countries in part due to differences in access to treatment and quality of the data sources across countries.[4,5] Prevalence of haemophilia is most accurately established in data from countries with national registries, as they are most likely to capture all cases and provide better quality data.[4,1,6] A study using high quality, established national patient registries in France, Italy, UK, Canada, Australia, and New Zealand was recently published with the aim to address these issues and provide more solid prevalence estimates.[6] The paper was based on data from established national patient registries in France, the UK, and Canada presented estimates of birth prevalence.[6] Final estimates were pooled, though the analyses were also repeated across the three registries with consistent results. The estimates of birth prevalence between 1991-2015 from this study are presented in Table 1.

Table 1. Estimated prevalence at birth (per 100,000 male births) of haemophilia A and haemophilia B, overall and limited to severe cases[a] for 1991-2015

	France	UK	Canada	Pooled (95% CI)
Haemophilia A				
Overall	24.0	24.6	19.1	23.2 (20.1-26.3)
Severe	8.6	10.2	9.9	9.4 (7.4-11.4)
Haemophilia B				
Overall	5.2	4.7	3.9	4.7 (3.4-6.1)
Severe	1.6	1.6	1.3	1.5 (0.7-2.3)

a. Adapted from Iorio et al., 2019

Estimates of prevalence of haemophilia A and haemophilia B from that study are presented in Table 2, with estimates from 2016 for Australia and Italy and from 2017 for the other four nations.

Table 2. Estimated prevalence (per 100,000 male births) of haemophilia A and haemophilia B, overall and limited to severe cases, by study country[a] for 2016 and 2017

	France	Italy	UK	Canada	Australia	New Zealand	Pooled (95% CI)
Haemophilia A							
Overall	17.8	13.6	19.8	18.5	18.4	14.1	17.1 (14.8-19.3)
Severe	5.8	6.1	5.9	5.8	6.0	6.2	6.0 (5.8-6.1)
Haemophilia B							
Overall	5.8	2.9	4.4	3.9	4.3	6.2	3.8 (3.2-4.4)
Severe	1.1	1.0	1.1	1.1	0.9	1.3	1.1 (1.0-1.1)

a. Adapted from Iorio et al., 2019

The authors noted that there was no significant heterogeneity in the prevalence of severe haemophilia across countries (although heterogeneity existed for mild and moderate haemophilia)[6]. The prevalence estimated by Iorio et al. (2019) was on the higher end of what has previously been cited in the literature for European counties. Previous prevalence

esitmates for haemophilia A range from 5.6 per 100,000 males in Estonia to 17.5 per 100,000 males in Hungary[4] , and the overall prevalence of haemophilia B (all severities) ranged from 0.47 per 100,000 males in Luxembourg to 8.07 per 100,000 in Ireland.[5]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

While publications presenting data on age distribution by severity for haemophilia in the EU are scarce, the available data generally report comparable age distributions across countries. The median age of patients with severe haemophilia (A and B) ranged between 28 to 35 years.[7,8,9]

One publication from the Austria nationwide haemophilia registry[7] presented data on age stratification for patients with severe haemophilia (Table 3).

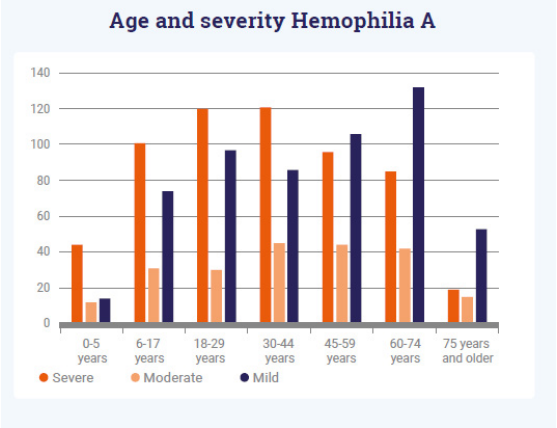
Table 3. Age distribution among patients with severe haemophilia A and severe haemophilia B in Austria as of 7 February 2016[a]

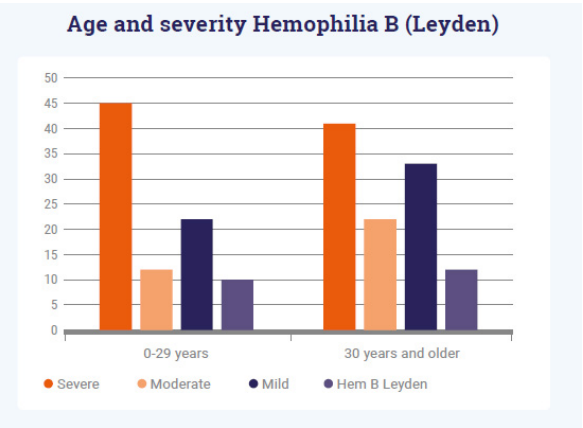
	Haemophilia A		Haemophilia B	
Age groups	**Number of patients N = 270**	**Percentage**	**Number of patients N = 24**	**Percentage**
0-10 years	36	13.3%	7	29.2%
11-20 years	61	22.6%	1	4.2%
21-30 years	48	17.8%	5	20.8%
31-40 years	55	20.4%	3	12.5%
41-50 years	47	17.4%	2	8.3%
51-60 years	9	3.3%	4	16.7%
61-70 years	12	4.4%	2	8.3%
71-80 years	2	0.7%	0	0
81-90 years	0	0	0	0
91-100 years	0	0	0	0

a. Adapted from Rejtő et al. 2019

The well-established Dutch nationwide haemophilia register, HemoNED, also presents age-specific data in bar graphs, without reporting exact numbers, in their annual report 2021, Figure 1 (HemoNED Foundation, 2022).

Figure 1 Number of patients by severity and age groups for haemophilia A (all patients: N=1376, severe disease: n=586) and haemophilia B (all patients: N=176, severe disease: n=86)[a]





Note: y-axis represent number of patients.
a. Reproduced from HemoNED Foundation, 2022

Median ages of patients with severe haemophilia A were similar across studies, ranging from 28 years in France,[9] to 35 years in Italy[8] . In the Austrian registry, conducted by Retjő and colleagues (2019), the median age was 28 years for severe haemophilia A or B (data not stratified). In the Dutch study using the HemoNED registry, age is presented as frequency by age groups (Figure 1), which illustrates that among patients with severe haemophilia A, patients in the age groups 18-29 and 30-44 accounted for about 20% each (approximately 120/586 for each age group), and patients in the age group 6-17 years accounted for about 17% (approximately 100/586) (HemoNED Foundation, 2022).

As fewer patients are diagnosed with haemophilia B, age estimates are based on much smaller sample sizes; however, findings are similar to that of the age distribution for severe haemophilia A, with the median age ranging from 30 years in France[9], to 32 years in Italy.[8] As noted previously, median age was 28 years for haemophilia A or B (data not stratified) in the Austrian registry.[7]

Gender

Since haemophilia is an X-linked hereditary disorder, almost all affected patients are male, whereas females are typically carriers only.[1] In the rare cases where females are affected, the disease is usually mild (Doncarli et al., 2019). Literature specific to females with haemophilia are limited. A study based on the French haemophilia registry, FranceCoag Network, reported 99.6% of patients with severe haemophilia A as male, whereas only 0.4% were female.[9] Among haemophilia B cases, 0.8% of severe cases were female (Doncarli et al., 2019).[9]

Race and Ethnicity

No epidemiologic data on race and ethnicity among patients with haemophilia in the EU populations was identified in the published literature. A recent US study, based on

surveillance data, found that the prevalence of haemophilia (A and B) was higher among whites (15.1 per 100,000 males) than either blacks (12.4 per 100,000 males) or Hispanics of either race (12.4 per 100,000 males).[10]

Risk factors for disease severity and morbidity

Haemophilia A is caused by numerous genetic defects in the F8 gene, which all differ significantly and are associated with different expressions of FVIII, both quantitatively and qualitatively.[11] Mutations leading to minimal, or no expression/production of the final protein will cause increased risk for bleeding and is classified as severe if the clotting FVIII activity level is less than 1% of normal levels.[2] Patients with severe haemophilia A exhibit the most severe bleeding phenotype with spontaneous bleeding into joints or muscles, whereas patients with moderate or mild haemophilia A bleed predominantly due to trauma.[11] Mutations leading to minimal, or no expression/production of the final protein (severe disease) are also deemed to be associated with higher risk of developing inhibitors.[12]

Besides the low levels of FVIII, there are additional factors that are thought to influence the clinical phenotype among patients with severe haemophilia A, including coinheritance of other bleeding or clotting disorders, pharmacokinetic handling of factor, physical activity patterns, and different treatment regimens. (Pavlova and Oldenburg, 2013; Carcao et al., 2013). Causality for environmetal factors can be complicated where, for example, physically active children might experience more traumatic bleeds, but on the other hand, muscle training and participating in sports can sustain joint function, and promote joint health.[11]

The risk factors for severe haemophilia B, are, to a large extent, similar to those in haemophilia A, but the pattern of underlying genetic mutations in the F9 gene less often result in severe haemophilia B (Dolan et al., 2018). Furthermore, fewer patients with haemophilia B develop inhibitors against infused coagulation factor, compared with patients with haemophilia A.[3]

The main existing treatment options:

Treatment of haemophilia is primarily achieved through replacement of the missing FVIII or FIX. The replacement factor products are commonly Standard Half-Life (SHL) or Extended Half-Life (EHL) recombinant factor products, but plasma-derived products of various purities are still in use. Treatment with the replacement coagulation factor can either be episodic, treating bleeding episodes on-demand as they occur, or prophylactic, preventing bleeding episodes by a regular schedule of FVIII or FIX infusions to maintain factor levels in a range >1%. Significant evidence exists that prophylactic treatment prevents bleeding episodes and the associated joint damage that is a major morbidity in haemophilic patients.[13,14,15,16,17]

Due to the relatively short half-lives of FVIII and FIX, effective prophylactic treatment in patients without inhibitors may require frequent IV administration, with the most frequent administration being every 2 days for SHL FVIII products, and up to twice weekly for SHL FIX products.[18,15,16,17] The recent development of EHL factor replacement products have helped reduce treatment burden for patients with haemophilia by lowering prophylactic

infusion rates and maintaining higher trough levels.[19,20,21] However, despite the approval of newer EHL products, patients still may require regular factor replacement IV infusions at frequencies ranging from twice weekly to once every 2 weeks.

Emicizumab (Hemlibra) is a bi-specific antibody that bridges activated coagulation Factor IXa and Factor X (to replace the function of missing activated FVIII). Hemlibra received approval by the FDA on 16 November 2017 for "routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors" and approval on 04 October 2018 "for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors".[22,23,24]

Hemlibra received approval by the EMA on 23 February 2018 for "routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors", "Hemlibra can be used in all age groups"[25] and on 11 March 2019 received approval for "routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors", and is currently approved for once weekly (QW) administration for the first 4 weeks, followed by SC administration weekly, or every 2 or 4 weeks.[26,27]

Hemlibra uses weight-based dosing and is supplied to the market in single-dose vials. Hemlibra has been developed exclusively for the treatment of haemophilia A patients and has no utility for haemophilia B patients.

Several newer treatments for haemophilia A or B are available in some markets or have submissions currently under regulatory review. Hemgenix (etranacogene dezxaparvovec-drlb in the USPI; etranacogene dezxaparvovec in the SmPC) is a gene therapy treatment recently approved in the US and conditionally approved in the EU for treatment of adults with haemophilia B.[28,29] Roctavian (valoctocogene roxparvovec) is a gene therapy treatment that has been recently approved in the US [30] and conditionally approved in the EU for the treatment of haemophilia A.[31] Alhemo (concizumab), a new monoclonal humanized IgG4 antibody that targets the K2 domain of TFPI, was approved in the EU in October 2024 and in the US in December 2024, also for hemophilia A and B patients with inhibitors.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The defining characteristic of both haemophilia A, and haemophilia B is bleeding, in particular, bleeding into large joints such as the elbows, knees, and ankles that eventually leads to painful and disabling haemophilic arthropathy (Berntorp et al., 2021).[1] The bleeding phenotype and natural history of patients with haemophilia A, and haemophilia B are generally comparable.[32] The most severe type of bleeding events is intracranial haemorrhage (ICH), which is most frequent in childhood (age ≤2 years), and in adults with known risk factors such as hypertension and age ≥60 years.[33] Wide ranges in incidence, and mortality among different cohorts have been reported across various studies assessing the occurrence of ICH among patients with haemophilia.[34] Among post-neonatal patients with haemophilia

who have been treated on demand, an estimated 3% to 10% experience an ICH during their life.[35]

Although recurrent bleeding is the hallmark of both haemophilia A and B, bleeding frequency may differ between the two forms of disease.[3] A study using single-center, retrospective chart review reported that bleeds occurred more frequently in patients with moderate-to-severe haemophilia A (14.4 bleeds/patient/year) compared with those with moderate-to-severe haemophilia B (8.63 bleeds/patient/ year).[36] In a large global study with patients treated per local routine clinical practice, the type of bleeding events among patients with severe haemophilia A ≥12 years old without inhibitors and without prophylaxis treatment, was reported as 73.5% bleeding in joints, 15.0% bleeding in the muscles, and 11.4% bleeding in the mouth or nose. The bleeding was caused by a traumatic event in 57.1% of the episodes.[37]

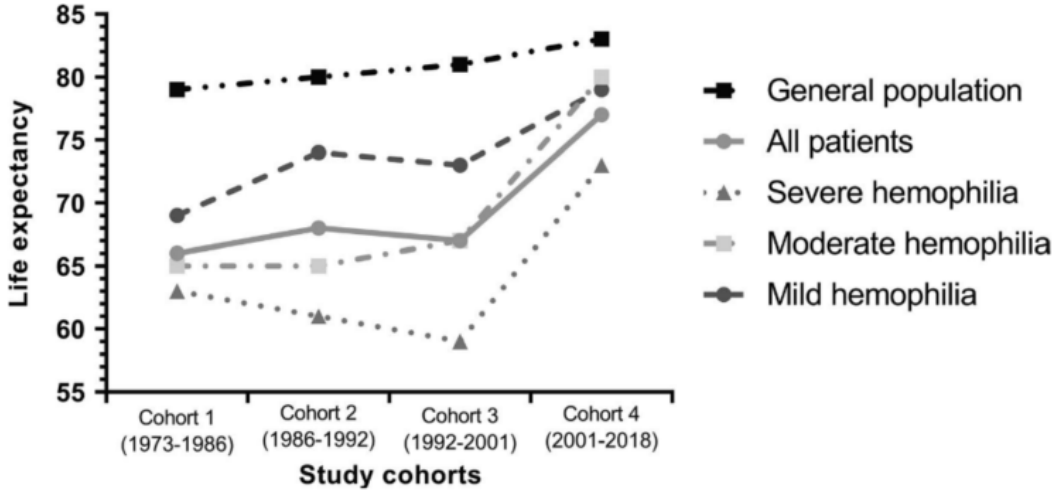
Although female populations are rarely affected by haemophilia, most often with mild disease, females with severe haemophilia may experience heavy menstrual bleeding and complications during or after pregnancy, including increased risk for post-partum haemorrhage.[38]

Mortality

Patients with haemophilia A or B have a higher death rate than the general population, and mortality increases with severity of disease (Berntorp et al., 2021). However, with better diagnostic tools and better treatment, death rates of patients with haemophilia have consistently decreased over time.[1,39]

In a recent study from the Netherlands, median life expectancy in the period of 2001-2018 among male patients with severe haemophilia (A and B) was estimated at 73 years.[40] This is a lower median life expectancy than male patients with moderate disease (80 years), mild disease (79 years), and the general Dutch male population (83 years) in the same time frame (Figure 2). Despite the lowest median life expectancy amongst male patients with severe haemophilia (A and B), the investigators highlight the 14-year gain in median life expectancy after 2001 (59 years in the 1992–2001 cohort compared to 73 years in the 2001–2018 cohort).[40]

Figure 2 Median life expectancy in patients with haemophilia in the Netherlands between 1973 and 2018[a]



a. Reproduced from Hassan et al. 2021

From 2001 to 2018, frequent causes of death among male patients with haemophilia in the Netherlands were non-hepatic malignancies (26%), and intracranial bleeding (14%). Ischemic stroke (1%), ischemic heart disease (2%), acquired immunodeficiency syndrome (AIDS; 2%), chronic liver disease (7%), and hepatocellular carcinoma (7%) were less frequent causes of death.[40] Mortality due to human immunodeficiency virus and hepatitis C virus infection among patients with haemophilia was reported to have decreased in the Netherlands over the past decades (Hassan et al., 2021).[40] From the same study, an increase in mortality due to intracranial haemorrhages was reported. No reason for this increase was identified, and the authors called for further studies to mitigate the risk for intracranial bleeding among patients with haemophilia. The same authors also called attention to the consistently low mortality rate due to ischemic heart disease (Hassan et al., 2021).[40]

Important co-morbidities:

The introduction of plasma-derived clotting factor concentrates as treatments for deficiency disorders was expected to improve the lives of patients with haemophilia; however, the initial applications of this treatment regimen preceded adequate safety measures and exposed many patients to Blood Borne Infections (BBIs).[41] As a result, a large proportion of patients with haemophilia were infected with HCV and/or HIV, among other BBIs, which further contributed to the morbidity and mortality experienced in this population.[41,1,42]

Due to the increasing life expectancy, age-related co-morbidities present new challenges in the management of patients with haemophilia. The most notable co-morbidities include hypertension, renal disease, and diabetes mellitus.[43,44,45,46] Haemophilia has been theorized to have a protective effect against mortality due to Cardiovascular Disease (CVD) (Hassan et al., 2021).[40] However, with the aging patient population, there has been an increase in CVD events among patients with haemophilia.[47]

Module SII. Non-Clinical Part of the Safety Specification

Nonclinical toxicity studies, summarized below, conformed with generally accepted scientific standards and guidelines at the time of study conduct and are considered adequate and sufficient for evaluation of the nonclinical safety of marstacimab (Table 4).

No additional nonclinical studies are considered warranted and there are no findings in the nonclinical testing that warrant inclusion among the summary of safety concerns, ie, reflective of an important identified risk or important potential risk, and there is no missing information.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Repeat-Dose Toxicity • Nonadverse effects were observed on the coagulation cascade in rats and cynomolgus monkeys and included decreases in fibrinogen, increases in D-dimer, changes in prothrombin time and activated partial thromboplastin time. • In rats only, nonadverse microscopic thrombi/emboli were observed at the injection site and lung.	Nonclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.
Reproductive/developmental toxicity • No effects on fertility were observed when marstacimab was administered as a repeat dose to male rats. • No effects were observed in male or female reproductive organs in the rat and cynomolgus monkey repeat-dose toxicity studies. • Developmental toxicity studies have not been conducted.	No hazards were identified for humans. Product labelling recommends that marstacimab should only be used during pregnancy or during breast-feeding if the potential benefit for the mother outweighs the risk to the foetus or breast-feeding child.
Genotoxicity Genotoxicity studies have not been conducted.	No genotoxicity data are available.
Carcinogenicity • Carcinogenicity studies have not been conducted.	No animal carcinogenicity data are available.
Safety pharmacology • No effects were observed on neurological parameters, respiration rate, ECG parameters, or haemodynamic endpoints in a repeat-dose toxicity study in cynomolgus monkeys.	No hazards were identified for humans.
Local Tolerance • Nonadverse reversible mixed cell infiltration, haemorrhage, and necrosis were observed at the injection sites in rats following subcutaneous administration.	No special hazards were identified for humans.
Other Toxicity Studies • In vitro studies evaluating human C1q and FcγR binding, cytokine release, and tissue cross-reactivity revealed no hazards for humans.	No hazards were identified for humans.

Table 4. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Pharmacology Studies • In vitro and in vivo studies with marstacimab and available bypass agents (eg, NovoSevenRT, FEIBA, or Byclot) support the concomitant use of marstacimab with these products. • Increased thrombin generation was seen with a combination treatment of marstacimab and emicizumab compared to marstacimab alone in hemophilia A plasma and was within the range of non-hemophilic normal plasma with or without marstacimab. These results are potentially supportive of sequential administration of emicizumab and marstacimab in hemophilia A patients switching between therapies.	No special hazards were identified for humans.

Module SIII. Clinical Trial Exposure

The indications of marstacimab are supported by safety information from a single Phase 3 study (B7841005). An open label extension (OLE) study (B7841007) is ongoing and provides a number of inhibitor and non-inhibitor participants that have completed the main Phase 3 Study (B7841005) and have qualified/consented to continue treatment in the long-term follow-up study. A supportive Phase 3 study (B7841008) , including ≥12 to <18 years of age with and without inhibitors participants that have qualified and consented to continue treatment in the long-term B7841007 follow-up study are included in the Table 5 Marstacimab Duration of Exposure.

A supportive Phase 1B study (B7841002) along with its respective OLE (B7841003) study evaluated a limited number of intended patient population participants at the 300 mg loading dose followed by one-weekly 150 mg marstacimab subcutaneous dose administration in this dose range finding study. The intended commercial presentation with the use of the pre-filled syringe was introduced later in the OLE study (B7841003). The Phase 3 study (B7841005) was conducted exclusively with the proposed dose (300 mg loading dose followed by once-weekly 150 mg marstacimab administered subcutaneously with a prefilled syringe). The participants that rolled over in the B7841007 study from the B7841008 study, ≥12 to <18 years of age, exclusively received 300 mg loading dose followed by once-weekly 150 mg marstacimab subcutaneously with the PFP or PFS.

Marstacimab dosing remains the same at 150 mg once-weekly or in some instances participants may have qualified for dose escalation to 300 mg once-weekly. Exposure to the intended commercial dose of marstacimab is presented in Table 5 from the B7841005 study.

Table 5. Marstacimab Duration of Exposure

Treatment duration	B7841005		B7841008		B7841007		B7841005/B7841007		B7841008/B7841007	
	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)
<1 Month	1	0.1	0		0		1	0.1	0	
≥1 Month to <3 Months	0		1	0.1	6	0.9	0		1	0.1
≥3 Months to <6 Months	3	0.8	0		7	2.2	3	0.8	0	
≥6 Months to <9 Months	3	2.2	1	0.5	8	5.3	3	2.2	1	0.5
≥9 Months to <12 Months	37	35.9	2	2	10	8.4	2	1.7	0	
≥12 Months to <18 Months	123	123.3	20	20	16	19.2	13	14.9	5	6.1
≥18 Months to <24 Months	0		0		18	30.9	9	15.7	8	13.9
≥24 Months to <30 Months	0		0		32	72.8	7	15.3	9	19.3
≥30 Months to <36 Months	0		0		49	131.9	19	51.3	0	
≥36 Months to <42 Months	0		0		27	85.3	31	101.2	0	
≥42 Months	0		0		2	7	79	305.7	0	
Total	167	162.3	24	22.6	175	363.9	167	508.9	24	40
Mean (SD)	1.0 (0.13)		0.9 (0.19)		2.1 (0.92)		3.0 (1.07)		1.7 (0.55)	
Median	1.0		1.0		2.4		3.4		1.8	
(Min, Max)	(0.1, 1.1)		(0.1, 1.0)		(0.1, 3.5)		(0.1, 4.5)		(0.1, 2.4)	

B7841005 Data cutoff date : 29Apr2025;B7841008 Data cutoff date : 26May2025; B7841007 Data cutoff date : 30May2025; Table Generation: 11SEP2025 (14:07)

Table 6. Marstacimab Cumulative Exposure by Age

Age (years)	B7841005		B7841008		B7841007		B7841005/B7841007		B7841008/B7841007	
	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)	Patients	Person Time (years)
<18	32	32	21	19.6	50	86.2	32	102.8	21	35.1
18-44	101	97.4	3	3	95	215.4	101	310.8	3	4.9
45-64	32	30.9	0		28	59.4	32	90.4	0	
65-74	1	1	0		1	2.7	1	3.7	0	

Age (years)	B7841005 Patients	B7841005 Person Time (years)	B7841008 Patients	B7841008 Person Time (years)	B7841007 Patients	B7841007 Person Time (years)	B7841005/B7841007 Patients	B7841005/B7841007 Person Time (years)	B7841008/B7841007 Patients	B7841008/B7841007 Person Time (years)
≥75	1	1	0		1	0.2	1	1.2	0	
Total	167	162.3	24	22.6	175	363.9	167	508.9	24	40
Mean (SD)		1.0 (0.13)		0.9 (0.19)		2.1 (0.92)		3.0 (1.07)		1.7 (0.55)
Median		1.0		1.0		2.4		3.4		1.8
(Min, Max)		(0.1, 1.1)		(0.1, 1.0)		(0.1, 3.5)		(0.1, 4.5)		(0.1, 2.4)

B7841005 Data cutoff date : 29Apr2025;B7841008 Data cutoff date : 26May2025; B7841007 Data cutoff date : 30May2025; Table Generation: 09SEP2025 (14:38)

Table 7. Marstacimab Cumulative Exposure by Ethnic Origin

Ethnic origin	B7841005 Patients	B7841005 Person Time (years)	B7841008 Patients	B7841008 Person Time (years)	B7841007 Patients	B7841007 Person Time (years)	B7841005/B7841007 Patients	B7841005/B7841007 Person Time (years)	B7841008/B7841007 Patients	B7841008/B7841007 Person Time (years)
Hispanic or Latino	13	12.8	0		13	31.9	13	44.8	0	
Not Hispanic or Latino	153	148.7	22	20.6	160	331.6	153	463.4	22	37.5
Not Reported	1	0.7	2	2	2	0.5	1	0.7	2	2.5
Total	167	162.3	24	22.6	175	363.9	167	508.9	24	40
Mean (SD)		1.0 (0.13)		0.9 (0.19)		2.1 (0.92)		3.0 (1.07)		1.7 (0.55)
Median		1.0		1.0		2.4		3.4		1.8
(Min, Max)		(0.1, 1.1)		(0.1, 1.0)		(0.1, 3.5)		(0.1, 4.5)		(0.1, 2.4)

B7841005 Data cutoff date : 29Apr2025;B7841008 Data cutoff date : 26May2025; B7841007 Data cutoff date : 30May2025; Table Generation: 15SEP2025 (10:34)

Table 8. Marstacimab Cumulative Exposure by Race

Race	B7841005 Patients	B7841005 Person Time (years)	B7841008 Patients	B7841008 Person Time (years)	B7841007 Patients	B7841007 Person Time (years)	B7841005/B7841007 Patients	B7841005/B7841007 Person Time (years)	B7841008/B7841007 Patients	B7841008/B7841007 Person Time (years)
Black or African American	9	9	6	6	15	15.3	9	18.4	6	11.9

Asian	86	83.2	14	13.5	91	189.5	86	262	14	24.2
White	71	69	4	3.1	68	158.1	71	226.3	4	3.9
American Indian or Alaska Native	0		0		0		0		0	
Not Reported	1	1	0		1	1.1	1	2.1	0	
Total	167	162.3	24	22.6	175	363.9	167	508.9	24	40
Mean (SD)		1.0 (0.13)		0.9 (0.19)		2.1 (0.92)		3.0 (1.07)		1.7 (0.55)
Median		1.0		1.0		2.4		3.4		1.8
(Min, Max)		(0.1, 1.1)		(0.1, 1.0)		(0.1, 3.5)		(0.1, 4.5)		(0.1, 2.4)

B7841005 Data cutoff date : 29Apr2025;B7841008 Data cutoff date : 26May2025; B7841007 Data cutoff date : 30May2025; Table Generation: 12SEP2025 (10:11)

Table 9. Marstacimab Cumulative Exposure by Haemophilia Type

Hemophilia Type	**B7841005 Patients**	**Person Time (years)**	**B7841008 Patients**	**Person Time (years)**	**B7841007 Patients**	**Person Time (years)**	**B7841005/B7841007 Patients**	**Person Time (years)**	**B7841008/B7841007 Patients**	**Person Time (years)**
Hemophilia A	131	126.4	18	16.6	136	287.6	131	400.2	18	30.5
Hemophilia B	36	35.9	6	6	39	76.4	36	108.7	6	9.5
Total	167	162.3	24	22.6	175	363.9	167	508.9	24	40
Mean (SD)		1.0 (0.13)		0.9 (0.19)		2.1 (0.92)		3.0 (1.07)		1.7 (0.55)
Median		1.0		1.0		2.4		3.4		1.8
(Min, Max)		(0.1, 1.1)		(0.1, 1.0)		(0.1, 3.5)		(0.1, 4.5)		(0.1, 2.4)

B7841005 Data cutoff date : 29Apr2025;B7841008 Data cutoff date : 26May2025; B7841007 Data cutoff date : 30May2025; Table Generation: 07SEP2025 (02:32)

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

There has been limited exposure in special populations to marstacimab and no epidemiologic studies have been conducted in pregnant/lactating women. Specific subpopulations were excluded from the clinical development programme. Paediatric patients ≥6 to <12 years are currently being evaluated in the ongoing Phase 3 clinical study B7841008. The following are the important exclusion criteria in the pivotal Phase 3 clinical study (B7841005) in participants ≥12 to <75 years of age development programme:

Efficacy Endpoints or Study Conduct Requirements

- Participants <12 years of age and >=75 years of age were not studied in the pivotal clinical study (B7841005).
- Participants with a body weight <35 kg at the time of signing informed consent were not studied in the pivotal clinical study (B7841005).
- Participants with haemophilia A with a FVIII activity ≥1% or haemophilia B with a FIX activity >2% were not studied in the pivotal clinical study (B7841005).
- Participants who were enrolled into the Non-Inhibitor Cohort in the pivotal Phase 3 clinical study (B7841005) could not have detectable or documented history of inhibitors (≥0.6 BU/mL or greater than the Upper Limit of Normal [ULN] for the testing laboratory) against FVIII or FIX prior to enrollment (Baseline of Observational Phase). These participants were not studied in the pivotal clinical study (B7841005).
- If non-inhibitor participants received routine prophylaxis (defined as treatment by IV injection of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement and did not demonstrate at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrolment and were not willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the Observational Phase, they were not studied in the pivotal clinical study (B7841005).
- Non-inhibitor participants receiving an on-demand treatment regimen with <6 acute bleeding episodes (spontaneous or traumatic, surgical bleeding episodes do not apply to this criterion) that required coagulation factor infusion during the 6 months period prior to Enrollment into Observational Phase or were not willing to continue to receive on-demand treatment during the Observational Phase were not studied in the pivotal clinical study (B7841005).
- Participants enrolled into the Inhibitor Cohort without documentation of current high titer inhibitor (≥5 BU/mL); or current low titer inhibitor (<5 BU/mL) refractory to FVIII or FIX replacement and with FVIII or FIX recovery <60% of expected within previous 6 months prior to Enrollment into Observational Phase were not studied in the pivotal clinical study (B7841005).
- Haemophilia A participants with inhibitors with on-demand treatment regimen with <6 bleeding episodes or haemophilia B participants with inhibitors with <4 bleeding episodes (spontaneous or traumatic, surgical bleeding episodes do not apply to this criterion) necessitating treatment with bypass factor during the 6 months prior to Enrollment into Observational Phase or not willing to continue to receive on-demand

treatment during the observational phase were not studied in the pivotal clinical study (B7841005).

- Participants who meet the bleeding criteria noted above and who are on routine prophylaxis (defined as treatment by iv injection of bypass factor to prevent bleeding) and have not demonstrated at least 80% compliance with scheduled prophylaxis regimen during the 6 months prior to enrollment, were not considered for eligibility in the pivotal clinical study (B7841005).
- Previous or current treatment for or history of coronary artery diseases, venous or arterial thrombosis (Common Terminology Criteria for Adverse Events [CTCAE][48] Grade >1), or ischemic disease (except for catheter associated-thrombosis) were not studies in the pivotal clinical study (B7841005).
- Participants with known haemostatic defects other than haemophilia A or B were not studied in the pivotal clinical study (B7841005).
- Abnormal renal or hepatic function as defined by the following laboratory results at Screening:
    a. Alanine transaminase (ALT) >2 × Upper Limit of Normal (ULN)
    b. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
    c. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention) is acceptable if the participant otherwise meets entry criteria
    d. Serum albumin less than the Lower Limit of Normal (LLN).
    e. Estimated Glomerular Filtration Rate (eGFR) <30 mL/min/1.73 m^2.

- Abnormal hematology values as defined by the following laboratory tests at Screening:
- Platelet count <100,000/uL
- Haemoglobin level <10 g/dL
- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
- QTcF >450 msec for male participants or QTcF >480 msec in participants with bundle branch block.

Prior/Concomitant Therapy:

- Current routine prophylaxis with bypassing agent (eg, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), non-coagulation non-factor replacement

therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of haemophilia.
    - Participants with inhibitors who are being treated using a prophylaxis treatment regimen with a bypass agent will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
    - Participants who have previously received non-factor-based haemophilia therapy (eg, fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
- Regular, concomitant therapy with immunomodulatory drugs (eg, IV Immunoglobulin [IVIG], and routine systemic corticosteroids, rituximab).
- Ongoing or planned use of immune tolerance induction during the Observational Phase or Active Treatment Phase, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the Active Treatment Phase.

Prior/Concurrent Clinical Study Experience:
- Participation in other studies involving investigational drug(s) or investigational vaccine(s) within 30 days (or as determined by local requirements) or 5 half-lives prior to study entry or during study participation.
- Previous exposure to PF-06741086 during participation in Studies B7841002 and B7841003.

Diagnostic Assessments:
- CD4 cell count ≤200/uL if Human Immunodeficiency Virus (HIV)-positive
- Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

Other Exclusion Criteria:
- Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

Reason for exclusion: These exclusion criteria were applied in the marstacimab clinical studies as participants with these backgrounds could confound efficacy assessments of adolescent and adult patients with severe Haemophilia A or severe Haemophilia B, or they could preclude completion of required study activities. Based on the mechanism of action of marstacimab, the study was designed to protect participants until additional clinical data could be obtained and evaluated to ensure that data collected in the clinical study to assess effects of marstacimab in the severe Haemophilia A or B populations were not confounded by pre-existing conditions.

Is it considered to be included as missing information? No.

Rationale: Use in patients with these types of conditions is not considered missing information because a different safety profile is not expected based on the clinical trial data. Marstacimab has no different risk profile for well characterized adverse reactions than marketed haemostatics.

Exclusion Criteria Related to Hypersensitivity to Marstacimab or to any of the Excipients

- Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.

Reason for exclusion: Unknown risk but standard wording for the administration of an endogenous substance.

Is it considered to be included as missing information? No

Rationale: There is no anticipated use of marstacimab where a patient has a known hypersensitivity reaction to marstacimab or any of its excipients as use in these patients is contraindicated.

Exclusion Criteria Related to Female

- Female participants were not studied in the development programme. There are no clinical studies of marstacimab use in pregnant women. Animal reproduction studies have not been conducted with marstacimab. It is not known whether marsatcimab can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. It is not known whether marstacimab is excreted in human milk. No studies have been conducted to assess the impact of marstacimab on milk production or its presence in breast milk.

Is it considered to be included as missing information? No

Rationale: Animal studies do not indicate direct or indirect harmful effects with respect to fertility. No fertility data are available in humans. Thus, the effect of marstacimab on male and female fertility is unknown. Because animal reproduction studies are not always predictive of human response, marstacimab should be used during pregnancy only if clearly needed. No further characterisation is therefore planned. Marstacimab should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the foetus taking into account that, during pregnancy and after parturition, the risk for thrombosis is increased and that several pregnancy complications are linked to an increased risk for Disseminated Intravascular Coagulation (DIC). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from marstacimab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

The following are the important exclusion criteria in the pivotal Phase 3 clinical study (B7841008) in participants 6 to <18 years of age development programme:

Age and Sex

- Females are not studied in the ongoing Study B7841008
- Participants age ≥18 years are not studied in the ongoing Study B7841008
- Participants ages 1 to <6 have not yet been studied in the ongoing Study B7841008, but are planned to be studied.
- Participants <19 kg are not studied in the ongoing Study B7841008.

Type of Participant and Disease Characteristics

- Participants with haemophilia A with a FVIII activity ≥1% or haemophilia B with a FIX activity >2% are not studied in the ongoing Study B7841008.
- Participants without at least 1 year of diary information and/or medical records available in which exogenous FVIII or FIX replacement or bypass agent infusions and hemophilic bleeding episodes were consistently documented over the 12 months prior to the time of informed consent/assent are not studied in the ongoing Study B7841008.
- Participants enrolled in the non-inhibitor cohort with detectable inhibitor (≥0.6 BU/mL at the central testing lab) against FVIII or FIX prior to Day 1 Pre-Dose are not studied in the ongoing Study B7841008.
- Participants enrolled in the non-inhibitor cohort with a documented history of high titer inhibitors (≥5 BU/mL or greater than the ULN for the testing laboratory) against FVIII or FIX in the 5 years prior to the time of informed consent/assent are not studied in the ongoing Study B7841008.
- Participants without inhibitors with <50 documented exposure days to FVIII/FIX replacement product are not studied in the ongoing Study B7841008.
- Participants without inhibitors who are not on a stable and effective routine prophylaxis regimen (defined as treatment by IV injection of factor concentrate to prevent bleeding) with FVIII/FIX replacement, based on local standard of care and in the opinion of the investigator, or have not demonstrated at least 80% compliance with that stable prophylaxis regimen are not studied in the ongoing Study B7841008.
- Participants enrolled into the Inhibitor Cohort without documentation of current high titer inhibitor (≥5 BU/mL); or current low titer inhibitor (<5 BU/mL) refractory to FVIII or FIX replacement and with FVIII or FIX recovery <60% of expected within previous 12 months prior to the time of informed consent/assent are not studied in the ongoing Study B7841008.
- Participants enrolled into the Inhibitor Cohort with Haemophilia A with on-demand treatment regimen with <12 bleeding episodes or hemophilia B participants with on-demand treatment regimen with <8 bleeding episodes (spontaneous or traumatic)

necessitating treatment with bypass factor in the 12 months prior to informed consent/assent are not studied in the ongoing Study B7841008.

- Participants enrolled into the Inhibitor Cohort with on-demand treatment <12 months prior to informed consent/assent are not studied in the ongoing Study B7841008.
- Participants enrolled into the Inhibitor Cohort with on-demand treatment without bleeding episodes documented over the previous 12 months prior to the time of informed consent/assent are not studied in the ongoing Study B7841008.
- Participants enrolled into the Inhibitor Cohort who are on routine prophylaxis (defined regularly scheduled and regimented administration by IV injection of bypass factor to prevent bleeding) and with < 80% compliance with scheduled prophylaxis regimen during the 12 months prior to the time of informed consent/assent are not studied in the ongoing Study B7841008.

Medical Conditions

- Participants with known coronary artery, thrombotic, ischemic disease, or current evidence of congenital or acquired thrombophilic disease are not studied in the ongoing Study B7841008.
- Participants with a known hemostatic defect other than hemophilia A or B are not studied in the ongoing Study B7841008.
- Participants with abnormal renal or hepatic function as defined by any of the following laboratory results at Screening are not studied in the ongoing Study B7841008:
    - ALT >2 × ULN.
    - Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
    - Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of HBsAg or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention) is acceptable if the participant otherwise meets entry criteria.
    - Serum albumin less than the LLN.
    - Participants (≥6 to <18 years) with estimated CrCl <30 mL/min/1.73 m^2 (by Modified Schwartz Equation performed by central lab.
- Participants with abnormal haematology values as defined by the following laboratory tests at screening are not studied in the ongoing Study B7841008:
    - Platelet count <100,000/uL
    - Haemoglobin level <10 g/dL
    - Fibrinogen level <LLN.
    - Prothrombin time >1.25 × ULN.
- Participants with other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or

investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
- Individuals with known allergic reaction or hypersensitivity to hamster protein or other components of the study intervention are not studied in the ongoing Study B7841008.

Prior/Concomitant Therapy

- Participants with current routine prophylaxis with bypassing agent (eg, aPCC, BYCLOT, PCC, or rFVIIa), non-coagulation non-factor replacement therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of haemophilia are not studied in the ongoing Study B7841008.
    - Participants with inhibitors who are being treated using a prophylaxis treatment regimen with a bypass agent will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
    - Participants who have previously received non-factor-based haemophilia therapy (eg, fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
- Participants with regular, concomitant therapy with immunomodulatory medications (eg, IVIG, routine systemic corticosteroids, rituximab) are not studied in the ongoing Study B7841008.
- Participants with use of systemic antifibrinolytic agents (eg, tranexamic acid, etc), medications that may increase the risk of bleeding (eg, aspirin, etc), and certain non-steroidal anti-inflammatory drugs (eg, ibuprofen, other COX non-specific NSAIDs, etc.) within 120 hours prior to the first dose of study intervention and throughout the duration of the study are not studied in the ongoing Study B7841008.
- Participants with ongoing or planned use of ITI, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention are not studied in the ongoing Study B7841008.

Prior/Concomitant Clinical Study Experience

- Participation in other studies involving investigational drug(s) or investigational vaccine(s) within 30 days (or as determined by local requirements) or 5 half-lives

prior to study entry or during study participation prohibits participation in the ongoing Study B7841008.
- Previous exposure to marstacimab during participation in other marstacimab clinical studies prohibits participation in the ongoing Study B7841008.

Diagnostic Exclusions

- Participants with CD4 cell count ≤200/uL if HIV-positive are not studied in the ongoing Study B7841008.
- Participants with a screening 12-lead ECG, interpreted by a central reader, that demonstrates clinically relevant abnormalities, in the opinion of the Investigator, that may affect participant safety or interpretation of study results are not studied in the ongoing Study B7841008.

Other Exclusions

- Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members are not studied in the ongoing Study B7841008.

Reason for exclusion:
These exclusion criteria were applied in the marstacimab clinical studies as patients with these backgrounds could confound efficacy assessments of adolescent patients with haemophilia A or haemophilia B with or without inhibitors or they could preclude completion of required study activities. Based on the mechanism of action of marstacimab, the B7841008 study was designed to protect patients until additional clinical data could be obtained and evaluated to ensure that data collected in the clinical study to assess effects of marstacimab in the patient population were not confounded by pre-existing conditions.

Is it considered to be included as missing information? No.

Rationale: Use in patients with these types of conditions is not considered missing information because a different safety profile is not expected based on the clinical trial data. No risks relevant to the proposed patient population have been identified.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 10. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	There are no clinical studies of marstacimab use in pregnant women. Animal reproduction studies have not been conducted with marstacimab. It is not known whether marstacimab can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. Marstacimab should be used during pregnancy only if the potential benefit for the mother outweighs the risk to the foetus taking into account that, during pregnancy and after parturition, the risk for thrombosis is increased and that several pregnancy complications are linked to an increased risk for Disseminated Intravascular Coagulation (DIC).
Breastfeeding women	It is not known whether marstacimab is excreted in human milk. No studies have been conducted to assess the impact of marstacimab on milk production or its presence in breast milk. Human IgG is known to be present in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from marstacimab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman
Fertility	Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3). No fertility data are available in humans. Thus, the effect of marstacimab on male and female fertility is unknown.
Paediatric population <12 years of age	There are limited data in paediatric patients < 12 years of age. The B7841008 paediatric study is on-going. Sixty-eight (68) patients from ≥6 to <12 years of age are currently enrolled and being treated. The adolescent population studied comprises a total of 24 patients (from ≥12 to < 18 years of age) in the B7841008 study, and 36 patients (from ≥12 to <18 years of age) were enrolled and treated in the B7841005 study. The safety profile of marstacimab was overall consistent between adolescents and adults.
Elderly population	Clinical studies of marstacimab did not include a sufficient number of patients aged 65 years and older to determine whether there are differences in exposure compared with younger patients (N = 1).
Body weight, age group, race, and haemophilia type	Although weight was an important covariate to describe the pharmacokinetics of marstacimab, no alteration in dosing is required due to weight in patients weighing ≥ 35 kg. Marstacimab clearance (CL/F) was 32% lower in adolescents (12 to < 18 years of age) compared to adults (18 years and older). After adjusting for weight, CL (L/hr/kg) in adolescents was estimated to be approximately 5% lower compared to that in adults, indicating that weight accounts for most of the differences in CL. This difference in PK did not translate to a clinically relevant difference in levels of the downstream pharmacodynamic marker peak thrombin between the 2 groups
Patients with hepatic impairment	Clinical studies have not been conducted to evaluate the effect of hepatic impairment on the PK of marstacimab, as it is generally not considered clinically relevant for mAbs. All patients with haemophilia A and B in the clinical studies had normal hepatic function (N = 204; total bilirubin and AST ≤ ULN) or mild hepatic impairment (N = 20; total bilirubin 1× to ≤ 1.5× ULN). Mild hepatic impairment did not affect the pharmacokinetics of marstacimab. No data are available on the use of marstacimab in patients with moderate or severe hepatic impairment.

Table 10. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with renal impairment	Renal clearance is not considered important for elimination of mAbs due to their large size and inefficient filtration through the glomerulus. Clinical studies have not been conducted to evaluate the effect of renal impairment on the PK of marstacimab. All patients with haemophilia A and B in the population pharmacokinetic analysis had normal renal function (N = 198; eGFR ≥ 90 mL/min/1.73 m^2) or mild renal impairment (N = 25; eGFR of 60 to 89 mL/min/1.73 m^2). Mild renal impairment did not affect the pharmacokinetics of marstacimab. There are no data available on the use of marstacimab in patients with moderate or severe renal impairment.
Subpopulations carrying relevant genetic polymorphisms	Characterization of the haemophilia genetic polymorphisms in participants within the marstacimab clinical trial program has not been conducted.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

SV.1.2. Exposure

The patient exposure for the cumulative period is estimated to be 16.60 patient years based on the sales of 867 Standard Units (SU) of marstacimab with the worldwide available sales in SUs provided by IQVIA from IBD (11 October 2025) through June 2025 and extrapolated through the end of the reporting period (30 August 2025). The sales of marstacimab from 01 July 2025 through 30 August 2025 were extrapolated by taking the average of sales of the previous 4 quarters.

The Average Daily Dose (AVDOS) is based on approved dosing regimens. For adults and adolescents, the maintenance dose is 150 mgSC weekly. AVDOS is intended to represent the average daily dose during maintenance therapy, not including the loading dose (which is a one-time administration). Accordingly, the AVDOS during maintenance therapy is 150 mg/week divided by 7 days, resulting in 21.43 mg/day. This value reflects the steady-state exposure and is appropriate for calculating patient-years. Given that exposure calculations are based on SU, the daily dose in SU is derived by dividing 21.43 mg/day by 150 mg/SU, yielding 0.143 SU/day. Therefore, patient-years are calculated using the formula: Total SU Sold ÷ (0.143 × 365.25).

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Marstacimab does not have characteristics that would make it attractive for use for illegal purposes; therefore, there is only a low potential for marstacimab misuse for illegal purposes.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

The safety concerns in the initial RMP are listed below:

Table 11. Summary of Safety Concerns in the Initial RMP

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Thromboembolism
Missing information	None

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP**:**

In clinical studies of marstacimab in severe haemophilia A or B adolescents (12 to < 18 years of age) and adults (18 years and older) patients, unintended events reasonably associated with the use of marstacimab included injection site reactions, which occurred in 13 (11.2%) patients. The term, Injection site reactions, was selected as the cluster term for the following MedDRA Preferred Terms (PTs): injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, injection site swelling. Injection site reactions is an ADR and its ADR frequency [Very common (≥ 1/10)] was categorized in accordance with the Council for International Organizations of Medical Sciences (CIOMS) III/V convention. [reference: Report of CIOMS Working Groups III and V. Guidelines for preparing core clinical-safety information on drugs. 2nd ed. 1999.]

Risk/Search Criteria	**Justification for Non-inclusion**
Injection site reactions (ISRs) include the following: injection site bruising, injection site erythema, injection site haematoma, injection site induration, injection site oedema, injection site pain, injection site pruritus, injection site swelling. Search criteria: HLT Injection site reactions	The identified risk of ISR is not considered important for inclusion as a safety concern for the purpose of risk management planning. The incidence rate of ISRs in the B7841005/B7841007 was 11.2%. Injection site pruritus 4 (3.4%) out of 116 participants was the most frequently reported ISR. ISRs tended to be mild in severity. Risk will be minimised via routine risk minimisation, with appropriate guidance included in the proposed SmPC to support administration and choice of location on the body to minimise the risk of injection site reaction. The proposed SmPC provides recommendation to rotate injection site at each. Guidance is also included in the proposed SmPC stating that the health care professional will show the patient how to use the prefilled pen or the prefilled syringe when

Risk/Search Criteria	Justification for Non-inclusion
	first used. Detailed instructions for use are included in the package leaflet and Instructions for Use document. The MAH will continue to monitor ISRs via routine pharmacovigilance, namely signal detection and adverse reaction collection, analysis, assessment, and reporting.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers:

Not applicable.

Known risks that do not impact the risk-benefit profile:

Not applicable.

Other reasons for considering the risks not important:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified: None.

Important Potential Risk 1: Thromboembolism

Embolic and thrombotic events (SMQ)

Important potential risks for patients with haemophilia A or B (without inhibitors) receiving treatment with marstacimab are formation/development of thromboembolism. Depending on location and severity, thromboembolism may be life-threatening or fatal. Patients should be made aware of the possible signs and symptoms associated with the development of deep venous thrombosis (eg, localized pain, swelling, redness of the foot, ankle or leg) and pulmonary embolism (eg, unexplained chest/shoulder pain or breathlessness) and seek urgent care promptly.

No cases of thromboembolic events were observed in haemophilia patients receiving marstacimab prophylaxis. The use of other anti-tissue factor pathway inhibitor (anti-TFPI) products has been associated with the development of thromboembolic complications. Marstacimab has not been studied in patients with a history of previous thromboembolic

events (see section 5.1 in the SmPC). Interrupt marstacimab prophylaxis if diagnostic findings consistent with thromboembolism occur and manage as clinically indicated.

Factor VIII and Factor IX products have been safely administered for the treatment of breakthrough bleeds in patients receiving marstacimab. If Factor VIII or Factor IX products are indicated in a non-inhibitor patient receiving marstacimab prophylaxis, the minimum effective dose of Factor VIII/Factor IX product according to the product label is recommended.

In nonclinical toxicity studies in rats and cynomolgus monkeys there were no adverse findings up to the highest doses tested, which were the maximum feasible doses for each species. Based on the nonclinical studies conducted, the coagulation cascade was identified as a potential target for marstacimab effects. Marstacimab-related effects on the coagulation cascade included nonadverse decreases in fibrinogen, increases in D-dimer, changes in prothrombin time and activated partial thromboplastin time, and, in rats only, microscopic thrombi/emboli in the tail vein injection site and lungs.

Consider the benefit and risk of using marstacimab in patients with a history of thromboembolic events.

Risk-benefit impact: Thromboembolic events may impact the risk-benefit profile of marstacimab due to the theoretical risk associated to long term treatment with anticoagulation therapies. The underlying risk varies according to the underlying diagnosis, associated comorbidities and treatments undertaken, the uncertainty in the long-term haemostatic effects associated with marstacimab. The benefit-risk balance for marstacimab in treating haemophilia A and haemophilia B patients without inhibitors at the recommended doses remains favourable.

Missing information: None

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Thromboembolism previously classified as important potential has been reclassified as important identified risk in the list of safety concerns.

Reasons for the reclassification to the list of safety concerns:

Thromboembolic events
Two venous thrombotic events were reported in clinical studies with marstacimab. One patient with haemophilia A in the open label extension study developed a deep vein thrombosis after approximately 3 years of marstacimab exposure. Marstacimab treatment was withdrawn and anticoagulant administered. The patient had multiple potential contributing factors including Factor V Leiden heterozygous gene mutation and lifestyle factors (ie, periods of extended immobilization and smoking).

In the Phase 1 study, one healthy participant with previously undiagnosed sarcoidosis developed a deep vein thrombosis and pulmonary embolism 9 days after receiving a single dose of 300 mg marstacimab and approximately 4 weeks after receiving a second dose of a vector-based (non-mRNA) COVID-19 vaccine (no longer available for use). Marstacimab was permanently discontinued, anticoagulant treatment was administered, and the adverse reactions resolved.

Benefits and Risks Conclusions

Marstacimab is a TFPI antagonist and may increase the risk of thromboembolic complications. Although the data for thromboembolic events is limited in the marstacimab clinical studies, there is evidence in the medical literature for the potential of a thrombotic event in hemophilia patients treated with an anti-TFPI agent. Health care providers should take into consideration the benefits and risks of using marstacimab in hemophilia patients with known risk factors for thromboembolism.

Based on the preceding information and given the potential mechanism of action to support a causal association between thrombosis and marstacimab, the MAH is reclassifying Thromboembolism (previously classified as an important potential risk) to an important identified risk in the list of safety concerns.

Based on the totality of data, with demonstrated efficacy and a favorable safety and tolerability profile, marstacimab continues to demonstrate a favorable benefit-risk profile when used in accordance with the approved indications.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Thromboembolism

Table 12. Thromboembolism

Potential mechanisms	Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events. In nonclinical toxicity studies in rats and cynomolgus monkeys there were no adverse findings up to the highest doses tested, which were the maximum feasible doses for each species. Based on the nonclinical studies conducted, the coagulation cascade was identified as a potential target for marstacimab effects. Marstacimab-related -related effects on the coagulation cascade included nonadverse decreases in fibrinogen, increases in D-dimer, changes in prothrombin time and activated partial thromboplastin time, and, in rats only, microscopic thrombi/emboli in the tail vein injection site and lungs.
Evidence source and strength of evidence	Arterial and venous thrombotic events, including embolism, were reported in clinical studies with marstacimab. These events occurred in individuals with multiple risk factors for thromboembolism. The following patients may be at an increased risk of thromboembolic events with use of this medicinal product: • patients with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease,

Table 12. Thromboembolism

	• patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (eg, Factor V Leiden), patients with prolonged periods of immobilization, obesity, and smoking, • patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer). • patients managed in perioperative setting and/or undergoing surgery. In the perioperative setting, concomitant use of Hympavzi with other haemostatic agents can potentially increase the risk of thrombosis.
Characterisation of the risk	Important identified risks for patients with haemophilia A or B (without or without inhibitors) receiving treatment with marstacimab are formation/development of thromboembolism. Depending on location and severity, thromboembolism may be life-threatening or fatal. Patients should be made aware of the possible signs and symptoms associated with the development of deep venous thrombosis (eg, localized pain, swelling, redness of the foot, ankle or leg) and pulmonary embolism (eg, unexplained chest/shoulder pain or breathlessness) and seek urgent care promptly. Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events. Arterial and venous thrombotic events, including embolism, were reported in clinical studies with marstacimab. These events occurred in individuals with multiple risk factors for thromboembolism. Precision estimate of thromboembolic events excludes a rate of 2.5 or higher per 100 treated individuals with 95% confidence. **Severity/Seriousness/Outcome** Two out of 167 (1.2%) participants experienced a thromboembolic event in the B7841007 open-label extension study. The event of "subclavian vein thrombosis" reported in one hemophilia A participant in the noninhibitor cohort was considered serious with a severity of Grade 3, severe, and the outcome for the participant was recovering. The event of "cerebral infarction" reported in one hemophilia A participant in the inhibitor cohort was considered serious with a severity of Grade 3, severe, and the outcome for the participant was not resolved.
Risk factors and risk groups	The incidence of venous thromboembolism and its complications increases with age: 1 case per 1,000,000 children aged <15 years; 72.4 cases per 100,000 adults aged 40 to 54 years; and 280 cases per 100,000 person who are from 85 to 89 years of age. Age-related changes occur in the vascular and haemostatic system, affecting platelet activity, coagulation factors, and coagulation inhibitors, as well as the endothelium. The fibrinolytic system is also impaired by aging, as is shown by increased levels of plasminogen activator inhibitor, which positively correlate with age-related pathological conditions such as diabetes, insulin resistance, and atherosclerosis. Advanced age is also accompanied by vessel stiffness and dilatation due to the degeneration of elastic fibers and increased collagen content and associated with a reduced expression of nitric oxide synthase thus leading to reduced NO production, which may contribute to platelet activation and thrombosis. Hyper-coagulability and

Table 12. Thromboembolism

	vascular wall changes together may increase the incidence of thrombotic events and pulmonary thromboembolism in the elderly patients.
Preventability	Identify patients with obvious risk factors for thromboembolism. The following patients may be at an increased risk of thromboembolic events with use of this medicinal product: • patients with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease, • patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (eg, Factor V Leiden), patients with prolonged periods of immobilization, obesity, and smoking,patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer). • patients managed in perioperative setting and/or undergoing surgery (see section 4.2). In the perioperative setting, concomitant use of Hympavzi with other haemostatic agents can potentially increase the risk of thrombosis. <u>Management in the perioperative setting</u> The safety and efficacy of marstacimab have not been formally evaluated in the surgical setting. Patients have had minor surgical procedures without discontinuing Hympavzi prophylaxis in clinical studies. For major surgery, it is recommended to pause Hympavzi at least 7 days prior and initiate management per local standard of care with clotting factor concentrate or bypassing agent and measures to manage the risk of venous thrombosis which can be elevated in the perioperative period. The product information for the clotting factor concentrate or bypassing agent should be consulted for dosing guidelines in patients with haemophilia undergoing major surgery. Resumption of Hympavzi therapy should take into account the overall clinical status of the patient, including the presence of post-surgical thromboembolic risk factors, use of other haemostatic products and other concomitant medicinal products (see Missed dose section above). A careful diagnostic approach is therefore essential. The first recommended step is to identify these patients with a low, intermediate, or high probability of being affected by thromboembolism. The benefits and risks of using Hympavzi in patients with a history of thromboembolic events, with known risk factors for thromboembolism, or currently experiencing an acute severe illness should be considered. Patients at risk should be monitored for early signs of thrombosis, and prophylactic measures against thromboembolism should be instituted according to current recommendations and standard of care. Hympavzi prophylaxis should be interrupted if diagnostic findings consistent with thromboembolism occur and patients should be managed as clinically indicated. The use of anti-tissue factor pathway inhibitor (anti-TFPI) products, including marstacimab, has been associated with the development of thromboembolic complications in patients exposed to additional haemostatic agents (ie, bypassing agents) in close proximity. Factor VIII and factor IX products and bypassing agents have been safely administered for the treatment of breakthrough bleeds in patients receiving marstacimab. If factor VIII or factor IX products or bypassing agents are indicated in a patient receiving Hympavzi prophylaxis, the minimum effective dose

Table 12. Thromboembolism

	according to the product label is recommended. Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events. In case of suspicion of thromboembolic events, Hympavzi should be discontinued and appropriate medical treatment should be initiated.
Impact on the risk-benefit balance of the product	Risk of thromboembolic events are known to hematologists. Based on the benefits of marstacimab for the approved indication and measures proposed to manage the risk of thromboembolism, the risk-benefit balance for marstacimab is considered favourable at the recommended dose in the approved indication.
Public health impact	Given the number of patients receiving anti-TFPI's, the impact to the public health is low.

Important Potential Risk: None

SVII.3.2. Presentation of the Missing Information

There is no missing information for marstacimab.

Module SVIII. Summary of the Safety Concerns

Table 13. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Thromboembolism
Important potential risks	None
Missing information	None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

  Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

  - ADR follow-up form for "Thromboembolic events" will be utilized. The adverse drug reaction follow-up forms are questions designed to obtain additional relevant information for the event of interest.

Other forms of routine pharmacovigilance activities for safety concerns:

None

III.2. Additional Pharmacovigilance Activities

Additional pharmacovigilance activities will include a long-term, Post-Authorization Safety Study (PASS) (B7841016) to evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort treated with marstacimab during routine clinical care.

Study short name and title:

B7841016: 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

Rationale and study objectives:

Based on publications and clinical trials of non-replacement therapies for haemophilia targeting TFPI pathways, thromboembolic events have been identified as a potential risk for monoclonal antibodies targeting TFPI pathways. To assess the potential risk of this primary safety event of interest among patients with severe haemophilia A or B who are treated with marstacimab in the real-world in Europe, an active surveillance study using data from several European haemophilia registers is proposed.

The primary study objective is:

- To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort treated with marstacimab during routine clinical care.

The secondary study objective is:

- To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort unexposed to marstacimab and receiving Standard-of-Care (SoC) treatment (eg, prophylaxis factor replacement).

- To describe clinical characteristics of patients (exposed to marstacimab and unexposed to marstacimab and receiving SoC treatment [eg, prophylaxis factor replacement]) who experience a thromboembolic event.

The safety event of interest, noted above, is based on current understanding of identified and potential risks with marstacimab. However, other safety events may be added/updated as understanding of the safety profile of marstacimab evolves and feasibility of their assessment permits.

Study design:

This is a multi-country, non-interventional, observational, prospective cohort study to evaluate the long-term safety of marstacimab in patients with severe haemophilia A or severe haemophilia B in a real-world setting in Europe. Data will be collected for up to 8 years from the start of the study. Patients may be included in the study at any time during this study period and will be followed until loss to follow-up in their originating register, death, or the end of the study.

Study Population:

Two patient cohorts will be included in the study:

- Patients with severe haemophilia A or severe haemophilia B who have been treated with marstacimab in a routine care setting after marstacimab has become commercially available in one or more European countries.

- Patients with similar severe haemophilia A or severe haemophilia B disease characteristics to those in the marstacimab exposure cohort but who are unexposed to marstacimab and receiving SoC treatment [e.g., prophylaxis factor replacement].

Additional comparator cohorts may be identified during the data source feasibility assessment, or cohorts may be added over time if the SoC changes or additional haemophilia treatments are approved.

Data Analysis:

Descriptive statistics will be presented. For categorical variables, the frequency and percent will be reported. For continuous variables, the mean, median, standard deviation, range, minimum, and maximum values will be presented.

All analyses will be conducted separately for each study cohort. The analyses will be performed for each register, and upon feasibility, a pooled analysis including data from all registers will also be conducted within each cohort.

Incidence rates and two-sided 95% CIs for safety outcomes will be estimated. Incidence rates will be calculated per 1,000 patient-years at risk. Time to first occurrence of the event will be calculated for safety outcomes, such as thromboembolic events. If possible, based on the feasibility assessment of core data elements collected in each register and the level of heterogeneity across the registers, subgroup analyses may be conducted. Incidence of thromboembolic events in the patient cohort unexposed to marstacimab will be conducted as a secondary analysis.

Details of the analysis will be provided in the protocol and the statistical analysis plan.

Milestones:

The study protocol will be submitted to the EMA within 6 months of marstacimab approval by the European Commission. An interim study report will be submitted 4 years after the start of data collection. Progress reports will be submitted as part of the PSUR which are prepared in accordance with the Guideline on GVP: Module VII – Periodic safety update report and the frequency of PSUR submission outlined in the European Union Reference Date List (EURD). The final study report will be submitted to regulatory agencies within 6 months after the end of data collection, tentative date subject to change of 30 June 2033.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 14. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
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 (B7841016) Planned	To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort treated with marstacimab during routine clinical care, relative to comparator cohorts treated with standard of care, such as factor replacement therapy, and unexposed to marstacimab.	Thromboembolic events	Protocol submission	Within 6 months of approval for marstacimab
			Interim/Progress Reports	Interim Report: 4 years after the start of data collection Progress reports to be reported with PSURs after start of data collection.
			Final Report	Within 6 months after end of data collection, anticipated 30 June 2035.

PART IV. PLANS FOR POST AUTHORISATION EEFICACY STUDIES

There are no post-authorisation efficacy studies planned for marstacimab.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Table 15. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
Important identified risks	
Thromboembolism	Routine risk communication: SmPC section 4.2, 4.4, 4.5 and 4.8 PL section 2
	Routine risk minimisation activities recommending specific clinical measures to address the risk: **SmPC Section 4.2 states**: Management in the perioperative setting The safety and efficacy of marstacimab have not been formally evaluated in the surgical setting. Patients have had minor surgical procedures without discontinuing Hympavzi prophylaxis in clinical studies. For major surgery, it is recommended to pause Hympavzi at least 7 days prior and initiate management per local standard of care with clotting factor concentrate or bypassing agent and measures to manage the risk of venous thrombosis which can be elevated in the perioperative period. The product information for the clotting factor concentrate or bypassing agent should be consulted for dosing guidelines in patients with haemophilia undergoing major surgery. Resumption of Hympavzi therapy should take into account the overall clinical status of the patient, including the presence of post-surgical thromboembolic risk factors, use of other haemostatic products and other concomitant medicinal products (see Missed dose section above). **SmPC Section 4.4 states:** Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events. Arterial and venous thrombotic events, including embolism, were reported in clinical studies with marstacimab (see Section 4.8). These events occurred in individuals with multiple risk factors for thromboembolism. The following patients may be at an increased risk of thromboembolic events with use of this medicinal product:

Table 15. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	• Patients with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease, • Patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (eg, Factor V Leiden), patients with prolonged periods of immobilization, obesity, and smoking, • Patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer). • patients managed in perioperative setting and/or undergoing surgery. In the perioperative setting, concomitant use of Hympavzi with other haemostatic agents can potentially increase the risk of thrombosis Marstacimab has not been studied in patients with a history of previous thromboembolic events (see section 5.1) and there is limited experience in patients with acute severe illness. The benefits and risks of using Hympavzi in patients with a history of thromboembolic events, with known risk factors for thromboembolism, or currently experiencing an acute severe illness should be considered. Patients at risk should be monitored for early signs of thrombosis, and prophylactic measures against thromboembolism should be instituted according to current recommendations and standard of care. Hympavzi prophylaxis should be interrupted if diagnostic findings consistent with thromboembolism occur and patients should be managed as clinically indicated. The use of anti-tissue factor pathway inhibitor (anti-TFPI) products, including marstacimab has been associated with the development of thromboembolic complications in patients exposed to additional haemostatic agents (ie, bypassing agents) in close proximity. Factor VIII and factor IX products and bypassing agents have been safely administered for the treatment of breakthrough bleeds in patients receiving marstacimab. If factor VIII or factor IX products or bypassing agents are indicated in a patient receiving Hympavzi prophylaxis, the minimum effective dose according to the product label is recommended. Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events. In case of suspicion of thromboembolic events, Hympavzi should be discontinued and appropriate medical treatment should be initiated. <u>Guidance on treating breakthrough bleeds</u> Factor VIII and factor IX products or bypassing agents (eg. rFVIIa or aPCC) can be administered for the treatment of breakthrough bleeds in patients receiving Hympavzi. Additional doses of

	Hympavzi should not be used to treat breakthrough bleeding events. Healthcare professionals should discuss with all patients and/or caregivers about the dose and schedule of the clotting factor concentrates or bypassing agents to use, if required, while receiving Hympavzi prophylaxis. When treating breakthrough bleeds with factor VIII or factor IX products or with bypassing agents, the lowest effective dose according to the product prescribing information is recommended. Healthcare professionals should refer to the product information for the clotting factor concentrate or bypassing agent being used. For rFVIIa, a maximum dose of 90 µg/kg body weight per dose and a maximum dosing frequency of every 2 hours is recommended. For aPCC, a maximum dose of 100 units/kg body weight within 24 hours is recommended. **SmPC Section 4.5 states:** **Interaction with other medicinal products and other forms of interaction** No clinical drug interaction studies with marstacimab have been conducted. Nonclinical in vitro pharmacodynamic drug interaction studies were conducted and support the concomitant use of marstacimab with bypassing agents (eg, rFVIIa or aPCC) for treatment of breakthrough bleeds. Combination of marstacimab with rFVIIa or aPCC (in haemophilia A and B plasma with inhibitors) resulted in increased thrombin generation compared to marstacimab treatment alone without exceeding peak thrombin levels achieved in non-haemophilic plasma treated with marstacimab alone; in some cases thrombin levels were within the range reported for non-haemophilic normal plasma. In general, no clinically meaningful differences in plasma peak thrombin have been observed in haemophilia patients who were on prophylactic marstacimab treatment with concomitant use of rFVIII, rFIX or bypassing agents including rFVIIa and aPCC in the Phase 3 study. Nonclinical in vivo pharmacodynamic drug interaction studies conducted in rats with normal FVIII and FIX levels also support the concomitant use of marstacimab with rFVIIa at a maximum clinical dose of ≤90 µg/kg or with aPCC at a maximum clinical dose of 100 units/kg for treatment of breakthrough bleeds. Increased incidence and/or severity of acute thrombi/emboli in the lung and injection site were observed in haemostatically normal rats at higher doses of rFVIIa (see section 5.3). For guidance on the use of clotting factor concentrates or bypassing agents for treatment of breakthrough bleeds in patients receiving marstacimab prophylaxis, see section 4.4. As a monoclonal antibody (mAb), marstacimab is expected to be cleared through catabolic pathways. Thus an impact on its

Table 15. Description of routine risk minimisation measures by safety concern

Safety Concern	Routine risk minimisation activities
	clearance via an interaction with concomitant medicinal products cleared via non-catabolic pathways is unlikely. Indirect effect of a biologic such as marstacimab on the expression of cytochrome P450 enzymes is also not expected. Other routine risk minimisation measures beyond the Product Information: None
Important potential risks: None	
Missing Information: None	

V.2. Additional Risk Minimisation Measures

Patient card

Objectives:

The objective of the Patient Card is to ensure that patients are reminded of the following regarding the risk for thromboembolism (blood clots) during treatment with marstacimab (Hympavzi):

The objective of the proposed aRMM is to provide an appropriate tool designed to enhance the awareness and knowledge of patients about the following safety concerns to ensure the optimal use of marstacimab.

- Key signs and symptoms of thromboembolism
- When to seek urgent attention from the healthcare provider or seek emergency help, should signs and symptoms of thromboembolism present themselves
- The prescribing physician's contact details

Rationale for the additional risk minimisation activity:

Additional awareness and knowledge of patients about the risks will help to mitigate these risks.

Target audience and planned distribution path:

The target audience is patients that will receive the material via their prescribing physician. The distribution plan may vary by local legal and regulatory requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Direct evaluation of the patient population is not planned due to known barriers to recruiting patients for survey research in the EU. The Patient Card is judged effective if no negative trends or worsening outcomes in the risk of thromboembolism are identified.

Removal of additional risk minimisation activities

Not Applicable

V.3. Summary of Risk Minimisation Measures

Table 16. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thromboembolism	Routine risk minimisation measures: SmPC section 4.4 and 4.8 PL section 2 Additional risk minimisation measures: Patient Card	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Adverse drug reaction follow-up forms Additional pharmacovigilance activities: B7841016: Voluntary PASS to further characterise the product's safety profile

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Hympavzi (marstacimab)

This is a summary of the RMP for Hympavzi. The RMP details important risks of Hympavzi, how this risk can be minimised, and how more information will be obtained about Hympavzi's risks and uncertainties (missing information).

Hympavzi’s Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Hympavzi should be used.

This summary of the RMP for Hympavzi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hympavzi's RMP.

I. The Medicine and What It Is Used For

Hympavzi is authorised for

Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- Haemophilia A (congenital factor VIII deficiency):
    - Without factor VIII inhibitors who have severe disease (FVIII < 1%)
    - With factor VIII inhibitors
- Haemophilia B (congenital factor IX deficiency):
    - Without factor IX inhibitors who have severe disease (FIX < 1%)
    - With factor IX inhibitors

It contains marstacimab as the active substance and it is intended for SC administration.

Further information about the evaluation of Hympavzi's benefits can be found in Hympavz's EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage link to the EPAR summary landing page.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Hympavzi, together with measures to minimise such risks and the proposed studies for learning more about Hympavzi’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*. In the case of marstacimab, the routine pharmacovigilance activities are supplemented with additional risk minimization measures mentioned under relevant important risk, below.

II.A List of Important Risks and Missing Information

Important risks of Hympavzi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hympavzi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table 17. List of important risks and missing information

Important identified risks	Thromboembolism
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Table 18. Important Identified Risk: Thromboembolism

Evidence for linking the risk to the medicine	Removal of TFPI inhibition may increase a patient's coagulation potential and contribute to a patient's individual, multifactorial risk for thromboembolic events. Two out of 167 (1.2%) participants experienced a thromboembolic event in the B7841007 open-label extension study.

Table 18. Important Identified Risk: Thromboembolism

	The event of "subclavian vein thrombosis" reported in one hemophilia A participant in the noninhibitor cohort was considered serious with a severity of Grade 3, severe, and the outcome for the participant was recovering. The event of "cerebral infarction" reported in one hemophilia A participant in the inhibitor cohort was considered serious with a severity of Grade 3, severe, and the outcome for the participant was not resolved. Arterial and venous thrombotic events, including embolism, were reported in clinical studies with marstacimab. These events occurred in individuals with multiple risk factors for thromboembolism. The following patients may be at an increased risk of thromboembolic events with use of this medicinal product: • Patients with a history of coronary artery disease, venous or arterial thrombosis or ischaemic disease, • Patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (eg, Factor V Leiden), patients with prolonged periods of immobilization, obesity, and smoking, • Patients currently experiencing an acute severe illness with increased tissue factor expression (such as serious infection, sepsis, trauma, crush injuries, cancer). • patients managed in perioperative setting and/or undergoing surgery (see section 4.2). In the perioperative setting, concomitant use of Hympavzi with other haemostatic agents can potentially increase the risk of thrombosis.
Risk factors and risk groups	The incidence of venous thromboembolism and its complications increases with age: 1 case per 1,000,000 children aged<15 years; 72.4 cases per 100,000 adults aged 40 to 54 years; and 280 cases per 100,000 person who are from 85 to 89 years of age. Age-related changes occur in the vascular and haemostatic system, affecting platelet activity, coagulation factors, and coagulation inhibitors, as well as the endothelium. The fibrinolytic system is also impaired by aging, as is shown by increased levels of plasminogen activator inhibitor, which positively correlate with age-related pathological conditions such as diabetes, insulin resistance, and atherosclerosis. Advanced age is also accompanied by vessel stiffness and dilatation due to the degeneration of elastic fibres and increased collagen content and associated with a reduced expression of nitric oxide synthase thus leading to reduced NO production, which may contribute to platelet activation and thrombosis. Hyper-coagulability and vascular wall changes together may increase the incidence of thrombotic events and pulmonary thromboembolism in the elderly patients. Refer to SVII 3.1
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.5 and 4.8 PL sections 2 Additional risk minimisation measures: Patient Card

Table 18. Important Identified Risk: Thromboembolism

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Voluntary Post Authorization Safety Study Short study name B7841016: 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 See section II.C of this summary for an overview of the voluntary post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of marstacimab.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name

B7841016: 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.

Purpose of the study:

Based on animal studies and clinical trials, thromboembolic events are an important potential risk associated with the use of marstacimab. To assess the potential risk of this primary safety event of interest among patients with severe haemophilia A or B who are treated with marstacimab in the real-world in Europe, an active surveillance study using data from several European haemophilia registers is proposed.

The primary study objective is:

- To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort treated with marstacimab during routine clinical care.

The secondary study objective is:

- To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort unexposed to marstacimab and receiving Standard-of-Care (SoC) treatment (eg, prophylaxis factor replacement).

- To describe clinical characteristics of patients (exposed to marstacimab and unexposed to marstacimab and receiving standard-of-care treatment [e.g., prophylaxis factor replacement]) who experience a thromboembolic event.

The safety event of interest, noted above, is based on current understanding of identified and potential risks with marstacimab. However, other safety events may be added/updated as understanding of the safety profile of marstacimab evolves and feasibility of their assessment permits.

PART VII. ANNEXES TO THE RISK MANAGEMENT

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Embolic and Thrombotic Events Questionnaire

MARSTACIMAB (HYMPAVZI) EMBOLIC AND THROMBOTIC EVENTS INFORMATION FOLLOW-UP QUESTIONNAIRE (FOR USE WITH HCPS)

You have received this follow-up questionnaire because, as a health care professional, you have reported a thrombosis or embolism identified event with Marstacimab. Please provide additional information below, if it is available to you. By providing this information, you are actively participating in safety monitoring of Marstacimab use.

1. Please provide the anatomical site of the thrombotic or embolic event:

2. Was the event venous or arterial?

☐ Venous ☐ Arterial

3. Please mark whether the patient had any of the following prior to start of therapy?

☐ Ischemic disease
☐ Coronary artery disease
☐ History of thromboembolism
☐ Blood coagulation disorders
☐ Tobacco use
☐ Oral contraceptives use
☐ Obesity
☐ Family history of thromboembolism
☐ Heparin use within 100 days of thrombosis
☐ Genetic prothrombotic conditions (e.g. Factor V Leiden)
☐ Immobilization at time of thrombosis
☐ Recent major trauma (e.g., hip fracture)
☐ Recent surgery
☐ Other relevant condition, please specify: _____

4. Were there alternative etiologies or explanations for the reported event(s)?

☐ Unknown

☐ No

☐ Yes (if yes, please specify) Details: _____

5. Please mark whether the patient had a relevant personal history of:

☐ Baseline deficiency of Factor VIII deficiency (Haemophilia A):
- ☐ Severe (<1%)
- ☐ Moderate (1-5%)
- ☐ Mild (>5%)

☐ Baseline deficiency of Factor IX deficiency (Haemophilia B):
- ☐ Severe (<1%)
- ☐ Moderate (1-5%)
- ☐ Mild (>5%)

6. Does the patient have other confounding medical conditions?

☐ *Yes* ☐ *No* ☐ *Unknown*
If Yes, please specify: _____

7. Please specify the following in relation to the product:

Pre-filled pen used? ☐ Yes or ☐ No
Lot number: _____ (please include a copy of the sticker, if available)
___ mg solution for injection in the pre-filled pen (please specify)
Expiry Date (dd-mmm-yyyy): ___ ___ / ___ ___ ___ / ___ ___ ___ ___
(please provide the expiry date if available)

Pre-filled syringe? ☐ Yes or ☐ No

Lot number: _____ (please include a copy of the sticker, if available)

___ mg solution for injection in the pre-filled syringe (please specify)

Expiry Date (dd-mmm-yyyy): ___ ___ / ___ ___ ___ / ___ ___ ___ ___

(please provide the expiry date if available)

Specify the product dose administered:

Please specify the following relative to the dose regimen at the time thrombosis was observed (mark all that apply):

Prophylaxis: mg/kg: _____ Frequency: _____

On Demand: mg/kg: _____ Frequency: _____

Estimated known number of exposure days: _____

8. Was the thrombosis at a catheter site?

☐ *Unknown*

☐ *No*

☐ *Yes*

9. For surgical patients experiencing thrombogenesis:

Type of surgery: _____

Thrombogenesis occurred: ☐ Yes or ☐ No

If yes, please specify:

☐ Before surgery ☐ During surgery ☐ After surgery

Were additional (unplanned) factor infusion (s) given? (Please specify all that apply.)

☐ Yes or ☐ No or ☐ Unknown

If yes, Dose: _____ Number of infusions: ____ Perioperative: _____

☐ Yes or ☐ No or ☐ Unknown

If yes, Dose: _____ Number of infusions: ____ During surgery: _____

☐ Yes or ☐ No or ☐ Unknown

If yes, Dose: _____ Number of infusions: ____ Post-operative: _____

Was marstacimab temporarily held? ___Prior to surgery ☐ Yes or ☐ No

Is yes, specify the number of days dose temporarily held prior to surgery: _____ (days)

____ Post-surgery ☐ Yes or ☐ No

If yes, specify the number of days dose temporarily held post-surgery: ____(days)

Patient's clinical status immediately post-operative? _____

Did the thrombogenesis event resolve: ☐ Resolved or ☐ Not resolved or ☐ Unknown

10. Please specify prior Factor replacement products that the patient has received (specify product, dose/regimen, total cumulative dose, start/stop, estimated or known number of exposure days):

_____

11. Was the patient on concomitant medications at the time of the event?

☐ Yes or ☐ No or ☐ Unknown

If yes (please specify): _____

Was the patient on herbal medicinal products?

☐ Yes or ☐ No or ☐ Unknown

If yes, please specify: _____

12. What is the patient's current clinical status? _____

13. Was the patient switched to another product?

☐ Yes or ☐ No or ☐ Unknown

If yes (please specify): _____

Start/Stop Dates (dd-mmm-yyyy): ___ ___ / ___ ___ ___ / ___ ___ ___ ___

- Regimen: _____
- Frequency: _____
- Reason for Switching: _____

14. Did the patient experience similar events/symptoms after the switch to another product?

☐ Yes or ☐ No ☐ Unknown

If yes, please provide the details: _____

Version History

Version	Version Date	Summary of Revisions
1.0		New form to describe special follow up requirement for marstacimab

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Key messages of the additional risk minimisation measures

Prior to the launch of Hympavzi in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the Patient Card including communication media and distribution modalities, with the National Competent Authority.

- The Patient Card is aimed at informing patients on the safe use of marstacimab and about the important risks associated with marstacimab. The Patient Card should be shared with the patient's healthcare professionals (HCPs) to inform the HCP of the patient's treatment with marstacimab and the risk of thromboembolic events.

The MAH shall ensure that in each Member State where Hympavzi is marketed, all HCPs and patients/carers who are expected to prescribe, use or oversee the administration of Hympavzi have access to/are provided with the Patient Card. The Patient Card will be translated in the local language to ensure understanding of proposed mitigation measures by HCPs and patients.

The Patient Card:

- Is to inform patients on the safe use of marstacimab and about the important risks associated with marstacimab.
- The patient should show the Patient Card to a doctor or a nurse whenever they have an appointment or go to the emergency room to seek care.
- Is to inform healthcare professionals that the patient is being treated with marstacimab.
- Reminds patients of the risk of thromboembolism during marstacimab treatment.
- Reminds the patient when and how they should seek medical advice for any symptoms suggestive of a thromboembolic event.
- Reminds patients when and how to report relevant signs and symptoms of thromboembolism.
- Provides contact details of the patient's marstacimab prescriber and emergency contacts.