11 October 2024
EMADOC-360526170-2060659
Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Hympavzi (marstacimab)
Treatment of haemophilia A

Sponsor: Pfizer Europe MA EEIG

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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The approved indication

Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or
- severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

Falls within the scope of the two designated orphan conditions "treatment of haemophilia A" and "treatment of haemophilia B".

The review of the criteria for the maintenance of the two respective orphan designations is covered in this one document.

2. Hympavzi for treatment of haemophilia A - EU/3/16/1752 (EMA/OD/0000179103)

2.1. Product and administrative information

Product	
Designated active substance(s)	Human monoclonal IgG1 antibody against tissue factor pathway inhibitor
Other name(s)	--
International Non-Proprietary Name	Marstacimab
Tradename	Hympavzi
Orphan condition	Treatment of haemophilia A
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Elsene Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pfizer Limited
COMP opinion	8 September 2016
EC decision	14 October 2016
EC registration number	EU/3/16/1752
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pfizer Limited to Pfizer Europe MA EEIG – EC decision of 19 November 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Daniela Philadelphy / Robert Porszasz
Applicant	Pfizer Europe MA EEIG
Application submission	6 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/006240
Invented name	Hemtivti
Therapeutic indication	Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: • severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors.
CHMP opinion	19 September 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Boje Kvorning Pires Ehmsen / Karri Penttila
Sponsor's report submission	23 May 2024
COMP discussion and adoption of list of questions	10-12 September 2024
Oral explanation	8 October 2024
Sponsor's removal request	9 October 2024
Sponsor's removal confirmation	11 October 2024

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing human monoclonal IgG1 antibody against tissue factor pathway inhibitor was considered justified based on pre-clinical in vivo data in a valid mouse model of the condition showing improved bleeding times;
- the condition is chronically debilitating due to recurrent bleeding in joints, gastrointestinal tract or in surgery, which may also be life-threatening;
- the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing human monoclonal IgG1 antibody against tissue factor pathway inhibitor will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate the effectiveness of a sub-cutaneous formulation in the treatment of the condition. The Committee considered that this constitutes a major contribution to patient care.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing human monoclonal IgG1 antibody against tissue factor pathway inhibitor as an orphan medicinal product for the orphan indication: treatment of haemophilia A.

2.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Haemophilia A is characterized by deficiency in factor VIII clotting activity that results in prolonged oozing after injuries, tooth extractions, or surgery, and delayed or recurrent bleeding prior to complete wound healing. The age of diagnosis and frequency of bleeding episodes are related to the level of factor VIII clotting activity. Haemophilia A is inherited in an X-linked manner. The risk to siblings of an individual proband depends on the carrier status of the mother. Carrier females have a 50% chance of transmitting the F8 pathogenic variant in each pregnancy: sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant are carriers. Affected males transmit the

pathogenic variant to all of their daughters and none of their sons. Carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible if the F8 pathogenic variant has been identified or if informative intragenic linked markers have been identified.

Individuals with severe haemophilia A are usually diagnosed during the first two years of life following bleeding from minor mouth injuries and large "goose eggs" from minor head bumps. Without prophylactic treatment, they may average up to two to five spontaneous bleeding episodes each month including spontaneous joint bleeds or deep-muscle hematomas, and prolonged bleeding or excessive pain and swelling from minor injuries, surgery, and tooth extractions. Individuals with moderate haemophilia A seldom have spontaneous bleeding; however, they do have prolonged or delayed oozing after relatively minor trauma and are usually diagnosed before age five to six years; the frequency of bleeding episodes varies, usually from once a month to once a year. Individuals with mild haemophilia A do not have spontaneous bleeding episodes; however, without pre- and postoperative treatment, abnormal bleeding occurs with surgery or tooth extractions; the frequency of bleeding episodes varies widely, typically from once a year to once every ten years. Individuals with mild haemophilia A are often not diagnosed until later in life. Approximately 30% of heterozygous females have clotting activity below 40% and are at risk for bleeding (even if the affected family member is mildly affected). After major trauma or invasive procedures, prolonged or excessive bleeding usually occurs, regardless of severity. The diagnosis of haemophilia A is established in a male proband by identification of decreased factor VIII clotting activity and a normal, functional von Willebrand factor level. (Konkle BA, Huston H, Nakaya Fletcher S. Hemophilia A. 2000 Sep 21 [Updated 2017 Jun 22]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.)

The approved therapeutic indication "Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or
- severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.

authorised therapeutic indication" falls within the scope of the designated orphan condition "Treatment of haemophilia A" and the orphan designation EU/3/23/2866 "treatment of haemophilia B".

Intention to diagnose, prevent or treat

The medical plausibility was confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The seriousness of the condition is acknowledged by the COMP. The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery, which may also be life-threatening.

Number of people affected or at risk

The sponsor has provided a prevalence estimate based on two approaches. The first establishes an estimate from the World Federation of Haemophilia. The number of EU/EEA patients diagnosed with haemophilia A, as determined by the 2013 and 2022 WFH Annual Global Survey, is estimated to be 31,754 (as seen in Table 1 below). Among the 30 countries included in the EU/EEA, a total of 25 are

represented here. Assuming a total population of 438.9 million in the EU/EEA as of 01 January 2022 (Eurostat, 2022), this is equivalent to 0.72 per 10,000 population.

Table 1. Prevalence Estimates for Haemophilia A

Country	Population	Haemophilia (n)	Haemophilia A (n)	Year of Data Collection
Austria	8,978,929	865	716	2022
Belgium	11,617,623	1,349	1,077	2022
Bulgaria[a]	-	-	-	-
Croatia	3,862,305	349	280	2022
Cyprus[b]	865,878	99	43	2013
Czech Republic	10,516,707	1,062	919	2022
Denmark[a]	-	-	-	-
Estonia	1,331,796	112	102	2022
Finland	5,548,241	310	180	2022
France	67,871,925	9,802	7,893	2022
Germany	83,237,124	5,087	4,245	2022
Greece	10,459,782	1,026	835	2022
Hungary	9,689,010	1,160	910	2022
Iceland[a]	-	-	-	-
Ireland	5,060,004	936	703	2022
Italy	59,030,133	3,651	2,944	2022
Latvia	1,875,757	119	96	2022
Lithuania	2,805,998	206	178	2022
Liechtenstein [a]	-	-	-	-
Luxemburg	645,397	20	16	2022
Malta[a]	-	-	-	-
Netherlands	17,590,672	1,778	1,535	2022
Norway	5,425,270	457	346	2022
Poland	37,654,247	3,231	2,754	2022
Portugal	10,352,042	1,028	818	2022
Romania	19,042,455	1,825	1,615	2022
Slovakia	5,434,712	717	622	2022
Slovenia	2,107,180	275	241	2022
Spain	47,432,893	2,129	1,842	2022
Sweden	10,452,326	1,066	844	2022
Total	**438,888,406**	**38,659**	**31,754**	

a. Not included in the 2022 WFH Annual Global Survey
b. Latest data available in the 2014 WFH Annual Global Survey
Source: WFH Report on the Annual Global Survey 2014

The second approach for the prevalence estimate uses incidence reported in the literature. Haemophilia is often calculated using only males in the denominator, the sponsor notes that they have not restricted their denominator in this way, in keeping with the goal of providing the most conservative estimate. In the EU/EEA, there were 8.7 live births per 1000 population (3.89 million live births) reported in 2022 (Eurostat. Number of Live Births, 2022). Applying 1 in 10,000 to total live births, this is equivalent to 389 newly diagnosed cases of haemophilia A in 1 year in the EU/EEA.

The sum of prevalent and incident cases (31,754 and 389, respectively) represents the total number of cases of haemophilia A during the year of this application (32,143). This is equivalent to 0.73 per 10,000 population.

The COMP could accept 0.7 in 10,000 as the final estimate for the purpose of the maintenance of the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor has provided a table (below) with all the approved medicines for haemophilia A in the European Economic Area.

Table 2. Overview of Authorized Medicinal Products for the Treatment of Haemophilia A

Trade name (MAH)	**Active substance**	**Countries where authorised**
Recombinant Factor-based Products		
Advate® (Baxter); Kovaltry® (Bayer); Recombinate® (Baxalta Innovations) Indication	Octocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Advate is indicated in all age groups. Kovaltry can be used in all groups.	EU centralised, IS, NO Recombinate: Nationally approved/approved in MRP
Posology and Method of Administration	20-40 IU/kg at intervals of 2-3 days Intravenous injection	
ReFacto AF® (Pfizer) Indication	Moroctocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ReFacto AF is appropriate for use in adults and children of all ages, including newborns. ReFacto AF does not contain von Willebrand factor, and hence is not indicated in von Willebrand's disease	EU centralised, IS, NO
Posology and Method of Administration	20-40 IU/kg at intervals of 2-3 days Intravenous infusion	
NovoEight® (Novo Nordisk) Indication	Turoctocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). NovoEight can be used for all age groups.	EU centralised, IS, NO

Posology and Method of Administration	20-40 IU/kg every second day or 20-50 IU/kg three times a week. In adults and adolescents (>12 years) a less frequent regimen (40-60 IU/kg every third day or twice weekly) may be applicable Intravenous injection	
Nuwiq® (Octapharma); Vihuma® (Octapharma) Indication	Simoctocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Nuwiq and Vihuma can be used for all age groups	EU centralised, IS, NO
Posology and Method of Administration	20-40 IU/kg at intervals of 2-3 days. Intravenous injection	
Afstyla® (CSL Behring) Indication	Lonoctocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Afstyla can be used for all age groups.	EU centralised, IS, NO
Posology and Method of Administration	20-50 IU/kg administered 2-3 times weekly Intravenous injection	
Adynovi® (Baxalta) Indication	Rurioctocog alfa pegol Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	EU centralised, IS, NO

Posology and Method of Administration	For bleeding episodes/surgery, 20 – 100 IU/dL with repeat injections every 12 to 24 hours. For long term prophylaxis, the recommended dose is 40 to 50 IU of ADYNOVI per kg bodyweight twice weekly in 3 to 4 day intervals. Intravenous use	
Elocta® (Sobi) Indication	Efmoroctocog alfa Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Elocta can be used for all age groups	EU centralised, IS, NO
Posology and Method of Administration	Prophylaxis: The recommended dose is 50 IU/kg at 3-5 day intervals. The dose may be adjusted based on patient response in the range of 25 to 65 IU/kg. Treatment of haemorrhage (20 – 100IU/dL), surgery (30-60 IU/dL) or major surgery (80-100 IU/dL), repeated every 12 to 24 hours or every 8 to 24 hours in life-threatening haemorrhages. Intravenous (IV) injection	
Jivi® (Bayer AG) Indication	Damoctocog alfa pegol Treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency).	EU centralised, IS, NO
Posology and Method of Administration	For bleeding episodes/surgery, 20 – 100 IU/dL with repeat injection every 24 – 48 hours. For prophylaxis the dose is 45-60 IU/kg every 5 days. Based on patient clinical characteristics the dose can also be 60 IU/kg every 7 days or 30-40 IU/kg two times per week. Intravenous use	

Esperoct® (Novo Nordisk) Indication	Turoctocog alfa pegol Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency).	EU centralised, IS, NO
Posology and Method of Administration	50 IU/kg every 4 days Intravenous injection	
NovoSeven® (Novo Nordisk) Indication	Eptacog alfa (activated) NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with inhibitors to coagulation FVIII or FIX >5 Bethesda Units (BU) • in patients with congenital haemophilia who are expected to have a high anamnestic response to FVIII or FIX administration • in patients with acquired haemophilia • in patients with congenital FVII deficiency • in patients with Glanzmann's thrombasthenia with antibodies to GP IIb – IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.	EU centralised, IS, NO
Cevenfacta® (LFB Biotechnologies) Indication	Eptacog beta (activated) CEVENFACTA is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII (i.e. ≥5 Bethesda Units (BU)); • in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII administration or expected to be refractory to increased dosing of FVIII.	EU centralised, IS, NO

Posology and Method of Administration	Treatment of mild/moderate bleeding episodes: 75 µg/kg repeated every 3 hours until haemostasis is achieved; or for severe Treatment of severe bleeding episodes: 225 µg/kg initially, followed if necessary 6 hours later with 75 µg/kg every 2 hours until haemostasis is achieved. Intravenous bolus injection	
Plasma-derived Factor Products		
Wilate® (Octapharma); Voncento ® (CSL Behring); Fanhdi®(Grifols); Optivate® (Bio Products Laboratory); Immunate® (Baxalta Innovations); Octanate® (Octapharma); Haemoctin® (Biotest Pharma) Indication(s)	Human plasma derived VWF; Human plasma derived coagulation factor VIII Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital FVIII deficiency). This product may be used in the management of acquired FVIII deficiency.	Nationally approved/nationally approved in MRP Voncento®: EU centralised, IS, NO
Posology and Method of Administration	Various doses e.g. Voncento Prophylaxis: The usual dose is 20-40 IU/kg at 2-3 day intervals. Treatment of haemorrhage (20 – 100IU/dL), minor surgery (30-60 IU/dL) or major surgery (80-100 IU/dL), repeated every 12 to 24 hours or every 8 to 24 hours in life-threatening haemorrhages and major surgery. Intravenous injection/infusion	

Non-Factor based Treatments		
Hemlibra® (Roche) Indication	Emicizumab Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency): • with factor VIII inhibitors • without factor VIII inhibitors who have: – severe disease (FVIII < 1%) – - moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype.	EU centralised, IS, NO
Posology and Method of Administration	3 mg/kg once weekly for the first 4 weeks (loading dose), followed by a maintenance dose from week 5, of either 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks Subcutaneous injection	
Gene Therapies		
Roctavian® (BioMarin International) Indication	Valoctocogene roxaparvovex Treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).	EU centralised, IS, NO
Posology and Method of Administration	6×10^{13} vg/kg vector genomes Single intravenous infusion	

Bypass Agents		
FEIBA® (Baxalta Innovations) Indication	Human coagulation FVIII inhibitor bypassing fraction *<u>Austria SmPC indications:</u>* • Treatment of bleeding in haemophilia A patients with inhibitors. • Treatment of bleeding in non-haemophiliacs with acquired inhibitors to FVIII. • Prophylaxis of bleeding in haemophilia A patients with inhibitors who have experienced a significant bleed or are at high risk of significant bleeding.	Nationally approved/nationally approved in MRP
Posology and Method of Administration	Prophylaxis: 70 – 100 U/kg every other day Treatment: 50 – 100 U/kg/bw. Repeat every 6 or 12 hours. Intravenous injection/infusion	

Notes:
1. Country codes: Iceland (IS), Norway (NO)
2. Indication presented is that obtained from UK SmPC unless otherwise stated
3. Data collected from EMA website, Heads of Medicines Agencies MRI Product Index and medicines.org website.

Currently there are guidelines from the World Haemophilia Federation. Srivastava A et al, WFH Guidelines for the Management of Hemophilia, 3rd edition Haemophilia. 2020;00:1–158.

The indication for the sponsor's product in haemophilia A is:

Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors,

The sponsor's proposed indication has complete overlap with that for Hemlibra, see table above. The following Factor VIII products are also considered satisfactory methods for the Hympavzi target patient population: Advate, Kovaltry, ReFacto AF, NovoEight, Nuwiq, Vihuma, Afstyla, Adynovi, Elocta, Jivi, Esperoct, Wilate, Voncento, Fanhdi, Immunate, Octanate and Haemoctin.

Significant benefit

The sponsor is proposing a claim of significant benefit based on clinically relevant advantage focused primarily on safety and a major contribution to patient care as their formulation is a subcutaneous injection.

The sponsor obtained scientific advice from CHMP 31 January 2019. Although they had an orphan designation from 2016, they did not raise a question on significant benefit with the COMP.

Several claims for a clinically relevant advantage are made by the sponsor to support significant benefit namely:

1. it is noninferior and superior to routine prophylactic factor-based replacement therapy for non-inhibitor haemophilia A patients.
2. Better efficacy in the haemophilia A adolescent (12-<18years) subpopulation.
3. Better clinical efficacy in haemophilia A due to required laboratory monitoring and occurrence of laboratory test interference with non-factor therapy.
4. Improved safety over existing haemophilia A therapies as particularly evident with the occurrence of thrombosis with Factor VIII and non-factor medicinal products.
5. Improved safety in terms of lower immunogenic potential over non-factor medicinal products.

The main study used to support the claims for a clinically relevant advantage is the pivotal phase 3 study B7841005. It should be noted that the sponsor has indicated that no patients were on Hemlibra or Roctavian in the run-in period.

This was a one-way, cross-over, open-label, multicentre study planned for approximately 145 adolescent and adult participants between the ages of 12 to <75years with severe haemophilia A or moderately to severe, to severe haemophilia B (defined as FVIII activity <1% or FIX activity < 2% respectively with or without inhibitor, with approximately 20% of participants as adolescents (aged between 12 to <18years old). This study was comparing treatment with the participants' prescribed factor replacement therapy or bypass therapy during an Observational Phase (OP) with a 12-month Active treatment Phase (ATP), during which participants were to receive marstacimab prophylaxis (defined as treatment by SC injection of marstacimab).

The inhibitor cohort included individuals who were receiving prior on-demand treatment (>45 participants, with at least 35 haemophilia A and 10 haemophilia B participants). The non-inhibitor cohort included >100participants with at least 80 haemophilia A and 20 haemophilia B participants.

Individuals without inhibitors who were receiving regimens of either prior on-demand or prior prophylaxis factor-based therapy (≥100 participants, with at least 80 haemophilia A and 20 haemophilia B participants. The results from the completed non-inhibitor cohort of Study B7841005 were provided in the MAA submission for marstacimab in October 2023.

Figure 1.

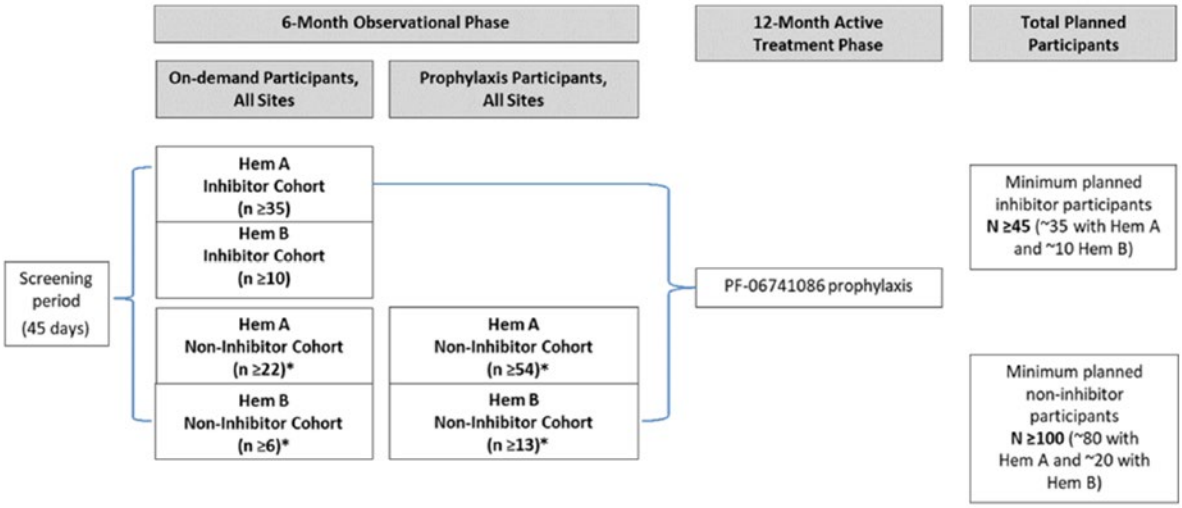


Table 3. Table B7841005 Protocol Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate the efficacy and safety of marstacimab for routine prophylaxis in severe haemophilia A or moderately severe to severe haemophilia B (FVIII:C <1% or FIX:C ≤2%, respectively) participants 12 to <75 years of age without inhibitors.	Primary efficacy endpoint: For the EU: non-inferiority of marstacimab versus prior prophylaxis using factor replacement as measured by the ABR of treated bleeds For regions outside the EU: superiority of marstacimab versus prior on-demand therapy using factor replacement as measured by the ABR of treated bleeds Primary safety endpoint (without alpha control): Adverse events (AEs) and serious adverse events (SAE)s Incidence and severity of thrombotic events; Immunogenicity Incidence and severity of injection site reaction Incidence of severe hypersensitivity and anaphylactic reactions Incidence and severity of thrombotic microangiopathy Disseminated intravascular coagulation/consumption coagulopathy Changes in physical examination and vital signs Incidence of clinically significant laboratory value abnormalities
Secondary	
Key objective: To evaluate additional efficacy of marstacimab; to evaluate the effect of marstacimab on HRQoL	Key secondary endpoints: Common endpoints for the EU and outside the EU Incidence of joint bleeds Incidence of spontaneous bleeds Incidence of target joint bleeds Incidence of total bleeds (treated and untreated) Physical health domain in Haem-A- QoL/Haemo-QoL Additional key secondary endpoints for the EU Total score in Haem-A-QoL EQ-5D-5L Index score EQ-5D-5L VAS score Included as key secondary endpoint for regions outside the EU is the non-inferiority of marstacimab versus prior prophylaxis using factor replacement in the ABR of treated bleeds, which is the primary endpoint for the EU.

For the EU, marstacimab prophylaxis was considered non-inferior to prior prophylaxis treatment if the upper bound of the 2-sided 95% confidence interval for the difference (ATP minus OP) in ABR was less than the non-inferiority boundary of 2.5. Note: this endpoint was evaluated as a secondary objective for regions outside of the EU.

For regions outside of the EU, marstacimab prophylaxis was considered superior to on-demand treatment with respect to ABR if the ABR ratio of marstacimab prophylaxis over on-demand treatment was lower than 0.5 at the 1-sided 0.025 level. (Note: this endpoint was evaluated as a secondary objective for the EU.) After establishing the superiority, non- inferiority of marstacimab versus prior prophylaxis was tested as part of key secondary endpoints.

During the active treatment phase in the study the following therapies were prohibited unless required for emergency management of acute breakthrough bleeds in the opinion of the investigator or treating physician.

- Non-inhibitor cohort: prophylaxis treatment with FVIII or FIX replacement or any use of bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).
- Inhibitor cohort: prophylaxis, on-demand, or preventative treatment with FVIII or FIX replacement therapy. Prophylaxis treatment with bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).

The primary analysis demonstrated non-inferiority of marstacimab prophylaxis compared to routine prophylaxis of OP. The mean ABR of treated bleeds in the non-inferiority cohort was 5.08 (95% CI.40,6.77) during the active treatment period compared to 7.85 (95% CI: 5.09, 10.61) during the observational period with routine prophylaxis, resulting in an estimated ABR difference of –2.77 (95% CI:-5.37, -0.16). Since non-inferiority was demonstrated, pre-specified statistical testing for superiority was performed and demonstrated superiority with a 2-sided p-value of 0.0376.

Discussion on claims for a clinically relevant advantage:

1. Marstacimab is noninferior and superior to routine prophylactic factor-based replacement therapy for non-inhibitor haemophilia A patients. It is understood that the on-demand superiority design of the trial was at the request of the FDA to reflect on practices in the US. It was clarified that marstacimab showed non-inferiority and statistical superiority over routine prophylactic factor-based therapy as measured by ABR of treated bleeds. The COMP however noted that patients were not on prior Hemlibra treatment before being included in the trial so a clinically relevant advantage based on efficacy can therefore not be concluded upon.
2. Better efficacy in the haemophilia A adolescent (12-<18years) subpopulation. The sponsor has made a claim of clinically relevant advantage based on fewer ABRs versus FVIIIs in adolescents versus adults. This was shown in such a small number of patients in the Phase III trial in direct comparison to Factor VIII replacement therapies that no conclusions can be drawn based on this data.
3. Better clinical efficacy in haemophilia A due to required laboratory monitoring and occurrence of laboratory test interference with non-factor therapy. Coagulation testing is conducted to help establish this. Marstacimab does not require monitoring of PK or PD laboratory values as part of routine monitoring or for dose adjustment. There is no direct or indirect comparison data to support this claim regarding Hemlibra apart from a reference to the SmPC. There is no evidence that the required laboratory monitoring would impact the efficacy for the patient, therefore a significant benefit cannot be concluded on.
4. Improved safety over existing haemophilia A therapies as particularly evident with the occurrence of thrombosis with Factor VIII and non-factor medicinal products. The sponsor has made a claim of a clinically relevant advantage regarding safety to Factor VIII products indicating that they have fewer thrombotic events. They have not however made a comparison to all adverse events between marstacimab and these products. The selective nature of the comparison does not offer an overall picture of the safety profiles and the data available for marstacimab is limited. The sponsor has also made a claim of a clinically relevant advantage regarding safety over Hemlibra but has not offered a comparison of serious adverse events or adverse event reporting. The comparison of post marketing pharmacovigilance data for Hemlibra, covers a much larger patient population than the limited number of patients covered in the clinical studies for marstacimab thus making a comparison regarding a better safety profile difficult to establish.

Major Contribution to Patient Care:

The sponsor has made one claims for major contribution to patient care:

1. *Over the challenging administration route, dosing, schedule, patient compliance, burden to patients and obstacles to implementation of prophylaxis that is associated with FVIII and emicizumab (Hemlibra) prophylaxis treatment.*

It should be noted that a claim for MCPC can only be accepted if it has been established that the product is at least equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products. The COMP accepts that this is the case of marstacimab over FVIII therapies, but the same conclusion cannot be drawn for Hemlibra.

The sponsor has not provided any conclusive data to Hemlibra to establish that there is at least equivalence regarding efficacy, safety and benefit/risk. The potential of a major contribution to patient care is claimed for their sub-cutaneous formulation in the context of the current delivery system for Hemlibra.

The sponsor provides a broad discussion regarding the major contribution to patient and they discuss a web-based survey of adults living with haemophilia (target n=200) and caregivers of children with haemophilia (target n=175) in the US and UK to quantify haemophilia treatment preferences.

The protocol for this survey is provided in the submission under Annex 3 titled B7841013 NON-INTERVENTIONAL STUDY PROTOCOL. This study aims to evaluate preferences of persons living with HA or HB or who care for adolescents living with HA or HB for a novel option for prophylaxis that is administered subcutaneously using a prefilled injection pen compared with other prophylaxes that use a different mode of administration. To reach the stated aim, this study has the following objectives: Primary Objectives:

- Quantify patients' and caregivers' preferences for administration, injection preparation and storage associated with routine prophylaxis for haemophilia.
- Quantify the risk patients and caregivers are willing to accept or the benefit patients and caregivers are willing to forgo in order to have their preferred administration method.

Secondary Objectives: Exploratory Objectives:

- Estimate the probability that patients and caregivers will choose different profiles representing current and future treatment options.
- Characterize unmet needs by examining patients' burden with the injection preparation and storage, and identify opportunities for improving the administration and injection/infusion process of haemophilia treatments.

This was a noninterventional, cross-sectional, double-blinded study. Following best practice, a mixed methods approach was used to iteratively develop and test a preference survey for quantitative preference elicitation that addresses the study objectives.

The survey included a discrete-choice experiment (DCE) to elicit preferences for multiple features of haemophilia treatment. While data collection is still on-going an interim analysis from patients and caregivers of haemophilia A (patients n=144; caregivers n=102) and B (patients n=26; caregivers n=22) indicates that the most important attributes to patients were dosing frequency (range: 3 fewer bleeds to 2 more bleeds). Risk of serious side effects (range: 0-5% risk during the next year of treatment), risk of developing inhibitors (range: 0-5% risk during the next year of treatment), and administration and device type (levels: intravenous infusion, subcutaneous via pre-filled pen and subcutaneous via draw up syringe) were the next most important attributes. Specifically, patients

preferred SC injections to IV infusions (P<0.001). Patients numerically preferred SC injection using a Pre-filled pen (PFP) to SC injection using a vial and syringe; however, this finding was not statistically significant. Refrigeration requirements was relatively less important to patients. Requiring a second treatment for breakthrough bleeds was unimportant to patients.

Among caregivers, dosing frequency was the most important treatment feature. The next most important features were changes in the number of bleeds per year and risk of serious side effects. Risk of developing inhibitors, administration mode, and refrigeration requirements were important, but somewhat less important to caregivers. Among the administration modes, SC injections were preferred to IV infusions. Requiring an additional treatment for breakthrough bleeds was unimportant to caregivers.

Less frequent dosing was preferred by both patients and caregivers. Both patients and caregivers did not differentiate between once weekly dosing and dosing every 2-4 weeks. Patient and caregiver preferences for SC injection over IV infusions and less frequent dosing as shown in the interim analysis are consistent with the results of the study by Garcia et al. 2024 and provide further evidence that the autoinjector is a major contribution to patient care.

Among the routes of administration included in the DCE, SC injection with a PFP was most preferred by patients when compared with SC injection with a syringe or IV infusions. Caregivers preferred SC injections to IV infusions. The auto-injector device may also enhance treatment adherence, as it reduces the burden and discomfort of administration. Moreover, the auto-injector device may facilitate home-based treatment which has the potential to improve patients' autonomy and reduce healthcare costs. These results suggest that the auto-injector device may represent a valuable option for patients and caregivers who seek a less burdensome way to deliver haemophilia treatment and, therefore, may constitute a major contribution to patient care.

Subcutaneous injection to intravenous solutions.

The interim analysis offers data which supports the major contribution of the sponsor's prefilled subcutaneous syringe to Factor VIII intravenous solutions. The survey clearly shows that patient preference was for subcutaneous injections to intravenous solutions. The finding in the interim analysis was statistically significant.

Prefilled subcutaneous syringe to draw up subcutaneous syringe

The sponsor has provided a summary of an interim analysis comparing a PFP which is the approached used with their device versus Hemlibra which requires delivery through subcutaneous injection via draw up syringe. The sponsor should be requested to further elaborate on the interim results between the two subcutaneous formulations and any additional data they may have to support this.

Conclusions

The COMP's position in view of the design of study B7841005 is to conclude that a clinically relevant advantage cannot be supported since there were no patients on prior treatment with Hemlibra in the run-in period.

The sponsor has not provided data regarding non inferior efficacy to Hemlibra and the data concerning better safety does not take into consideration a comparison to the full adverse event profiles. It is therefore difficult to establish if there is a clinically relevant advantage.

Major contribution to patient care between intravenous solutions the delivery system of choice for factor VIII products and subcutaneous injections has been established through the interim analysis provided in the discrete-choice experiment B7841013 NON-INTERVENTIONAL STUDY PROTOCOL.

Major contribution to patient care between two different subcutaneous delivery methods: a prefilled pen (auto-injector device) which is what the sponsor's product uses and a draw up syringe which is the system used for Hemlibra has also been discussed. They noted that patients numerically preferred SC injection using a pre-filled pen (PFP) to SC injection using a vial and syringe; however, this finding was not statistically significant. Any additional data to further elaborate on this finding should be provided.

2.4. COMP list of issues

- Significant Benefit:

In order to establish major contribution to patient care, the product should be at least equivalent in terms of efficacy, safety and benefit/risk balance as compared with the authorised medicinal products. The sponsor should therefore provide relevant comparative efficacy data of their product versus Hemlibra.

The sponsor is requested to further elaborate on the clinical data used to support the claim of major contribution to patient care between their subcutaneous delivery system and the formulation used to deliver Hemlibra. Further elaboration with clinical data should be provided regarding improving patient quality of life and physical activity.

3. Hympavzi for treatment of haemophilia B - EU/3/23/2866 (EMA/OD/0000179102)

3.1. Product and administrative information

Product	
Designated active substance(s)	Marstacimab
Other name(s)	--
International Non-Proprietary Name	Marstacimab
Tradename	Hympavzi
Orphan condition	Treatment of haemophilia B
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Elsene Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pfizer Limited
COMP opinion	9 November 2023
EC decision	13 December 2023
EC registration number	EU/3/23/2866
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Daniela Philadelphy / Robert Porszasz
Applicant	Pfizer Europe MA EEIG
Application submission	6 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/006240
Invented name	Hympavzi
Therapeutic indication	Hympavzi is indicated for 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 factor IX inhibitors.
CHMP opinion	19 September 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Boje Kvorning Pires Ehmsen / Karri Penttila
Sponsor's report submission	23 May 2024
COMP discussion	10-12 September 2024
Sponsor's removal request	9 October 2024
Sponsor's removal confirmation	11 October 2024

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2023 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing marstacimab was considered justified based on preliminary clinical data showing a significant reduction in annual bleeding rate;
- the condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury. Bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening;
- the condition was estimated to be affecting approximately 0.17 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing marstacimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a significant reduction in annual bleeding rate in patients with severe haemophilia B who no longer respond to treatment adequately. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing marstacimab as an orphan medicinal product for the orphan condition: treatment of haemophilia B.

3.3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Haemophilia B is an X-linked congenital bleeding disorder, characterized by a decrease in Factor IX - plasma levels that produce a variety of bleeding symptoms of different severity. The condition accounts for 10-15% of the total haemophilia patients and predominantly affects males. Haemophilia B is caused by heterogeneous mutations in the FIX gene and is divided into three categories according to the coagulation factor activity present in blood: severe (<1% of normal circulating FIX), moderate (1–5% of normal circulating FIX), or mild (>5% to <40% of normal circulating FIX). Most bleeding occurs

internally, into the joints or muscles and some bleeds can be life-threatening and require immediate treatment, generating relating complications: chronic synovitis, muscular atrophy, sites of bleeding in depth. Clinically apparent bleeding in haemophilia B typically correlates with the factor IX activity in

plasma, although some patients may have variability in phenotypic bleeding with up to 10% of severe patients with a mild phenotype.

With the deficiency of FIX, activation of FX becomes severely impaired; in consequence, the thrombin burst becomes delayed and insufficient for normal haemostasis. The haemostatic plug formed for affected patients is therefore fragile and easily dissolved by normal fibrinolytic activity, leading to impaired haemostasis and prolonged bleeding episodes.

The approved therapeutic indication "Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with:

- *severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or*
- *severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors.*

falls within the scope of the designated orphan condition "Treatment of haemophilia B".

Intention to diagnose, prevent or treat

The medical plausibility was confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The condition is considered life-threatening and chronically debilitating by the COMP due to spontaneous bleeding episodes and substantially prolonged bleeding upon injury. Bleeding starts early in life and can include life threatening haemorrhages, such as intracranial and gastrointestinal haemorrhages. Adult patients are at risk for cerebral- or gastric haemorrhage, which can be life-threatening.

When severe, the disease leads to spontaneous life-threatening bleeding episodes leading to deaths and morbidity from chronic joint disease. When untreated, most individuals with severe haemophilia die from bleeding complications before 25 years of age. Compared to the general population, all-cause mortality is higher (by a factor of 2.69), and median life expectancy is lower (15 years less). Even in the era of adequate factor replacement products, the hallmark of haemophilia B is the lifelong propensity for bleeding.

Since designation, there have been no changes in the chronically debilitating or life-threatening nature of haemophilia B.

Number of people affected or at risk

The sponsor has provided two sources for their prevalence estimate. The first is based on the World Federation of Haemophilia reports from, 2014, 2018, 2022. The number of EU/EEA patients diagnosed with haemophilia B, as determined by the 2014, 2018 and 2022 WFH Annual Global Survey, was estimated to be 6,902 (as seen in Table 1). Among the 30 countries included in the EU/EEA, a total of 27 are represented here. Assuming a total population of 445.2 million in the EU/EEA as of 01 January 2022 (Eurostat, 2022), this is equivalent to 0.16 per 10,000 population.

Table 4. Prevalence Estimates for Haemophilia B

Country	Population	Haemophilia (n)	Haemophilia B (n)	Year of Data Collection
Austria	8,978,929	865	149	2022
Belgium	11,617,623	1,349	265	2022
Bulgariaa	-	-	-	-
Croatia	3,862,305	349	69	2022
Cyprus	858,000	99	56	2014
Czech Republic	10,516,707	1,062	143	2022
Denmark	5,781,190	490	102	2018
Estonia	1,331,796	112	10	2022
Finland	5,548,241	310	34	2022
France	67,871,925	9,802	1,909	2022
Germany	83,237,124	5,087	842	2022
Greece	10,459,782	1,026	191	2022
Hungary	9,689,010	1,160	250	2022
Icelanda	-	-	-	-
Ireland	5,060,004	936	233	2022
Italy	59,030,133	3,651	707	2022
Latvia	1,875,757	119	23	2022
Lithuania	2,805,998	206	28	2022
Liechtensteina	-	-	-	-
Luxemburg	645,397	20	4	2022
Maltaa	520,971	37	-	2022
Netherlands	17,590,672	1,778	243	2022
Norway	5,425,270	357	111	2022
Poland	37,654,247	3,231	477	2022
Portugal	10,352,042	1,028	210	2022
Romania	19,042,455	1,825	210	2022
Slovakia	5,434,712	717	95	2022
Slovenia	2,107,180	275	34	2022
Spain	47,432,893	2,129	287	2022
Sweden	10,452,326	1,066	220	2022
Total	**445,182,689**	**39,086**	**6,902**	

a: WFH Report on the Annual Global Survey 2014, 2017, 2018, 2020 & 2021

In their second estimate the sponsor notes that the incidence of haemophilia in the EU/EEA population is reported to occur in around 1 in 10,000 live male births each year (WFH about bleeding disorders, 2012). Haemophilia B occurs less frequently than haemophilia A, at a rate of 1 in 30,000 male births (Giannelli et al, 1998) and 5 in 100,000 male births (Iorio et al, 2019). While haemophilia is often calculated using only males in the denominator, the sponsor has not restricted their denominator in this way, in keeping with the goal of providing the most conservative estimate. In the EU/EEA, there were 8.7 live births per 1,000 population (3.89 million live births) reported in 2022 (Eurostat. Number of Live Births, 2022).

Applying 1 in 30,000 or 5 in 100,000 to total live births, this is equivalent to between 130 – 194 newly diagnosed cases of haemophilia B in one year in the EU/EEA. The sum of prevalent and incident cases

(6,902 and (130 or 194), respectively) represents the total number of cases of haemophilia B (between 7,032 – 7,096) during the year of this application. This is equivalent to about 0.16 per 10,000 population.

Both estimates come to 0.16 in 10,000 which could be accepted by the COMP for the purpose of maintaining the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor has provided a table listing the authorised medicines in the European Economic Area. These are summarised in Table 2 below.

Table 5. Overview of Authorized Medicinal Products for the Treatment of Haemophilia B

Trade name (MAH)	**Active substance**	**Countries where authorised**
Gene Therapies		
Hemgenix® (CSL Behring GmbH)	Etranacogene dezaparvovec	EU centralised, IS, NO
Indication	Treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.	
Posology and Method of Administration	Single dose of 2 x 10^{13} gc/kg Intravenous infusion	
Recombinant Factor-based Products		
BeneFIX® (Pfizer)	Nonacog alfa	EU centralised, IS, NO
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). BeneFIX can be used for all age groups.	
Posology and Method of Administration	40 IU/kg at intervals of 3 to 4 days Intravenous infusion	
RIXUBIS® (Baxalta Innovations)	Nonacog gamma	EU centralised, IS, NO
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). RIXUBIS is indicated in patients of all age groups.	
Posology and Method of Administration	40 to 60 IU/kg at intervals of 3 to 4 days Intravenous use	
ALPROLIX® (Swedish Orphan Biovitrum AB)	Eftrenonacog gamma	EU centralised, IS, NO
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). ALPROLIX can be used for all age groups.	
Posology and Method of Administration	Starting regimens of 50 IU/kg or 100 IU/kg once every 10 days Intravenous injection	

IDELVION® (CSL Behring GmbH)	Albutrepenonacog gamma	EU centralised, IS, NO
Indication	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency). IDELVION can be used for all age groups.	
Posology and Method of Administration	35 to 50 IU/kg once weekly Intravenous injection	
ReFixia® (Novo Nordisk)	Nonacog beta pegol	EU centralised, IS, NO
Indication	Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia B (congenital factor IX deficiency)	
Posology and Method of Administration	40 IU/kg once weekly Intravenous injection	
NovoSeven® (Novo Nordisk)	Eptacog alfa (activated)	EU centralised, IS, NO
Indication	NovoSeven is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with inhibitors to coagulation factors VIII or IX > 5 BU • in patients with congenital haemophilia who are expected to have a high anamnestic response to FVIII or FIX administration • in patients with acquired haemophilia • in patients with congenital FVII deficiency • in patients with Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available.	
Posology and Method of Administration	Not approved for prophylaxis; 90 µg/kg for bleeding episode Intravenous bolus injection	

Cevenfacta® (Laboratoire Francais du Fractionnement et des Biotechnologies)	**Eptacog beta (activated)**	**EU centralised, IS, NO**
Indication	Cevenfacta is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU)); • in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.	
Posology and Method of Administration	Not approved for prophylaxis; 75 to 225 µg/kg for bleeding episode Intravenous bolus injection	
Plasma-derived Factor Products		
AlphaNine® (Grifols); Haemonine® (Biotest); Mononine® (CSL Behring); Octanine® (Octapharma); Replenine-VF® (Bio Products Laboratory)	Human plasma derived coagulation factor IX	Nationally approved/nationally approved in MRP
Common indication	Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency).	
Posology and Method of Administration	Various doses Intravenous use	

Bypass Agents		
FEIBA® (Shire Pharmaceuticals)	Human plasma proteins with factor VIII inhibitor bypassing fraction.	Nationally approved/nationally approved in MRP
Indication	*Indications in some countries, including Austria:* Treatment of bleeding in haemophilia A patients with inhibitors. Treatment of bleeding in haemophilia B patients with inhibitors, if no other specific treatment is available (see SmPC section 5.1). Treatment of bleeding in non-haemophiliacs with acquired inhibitors to factor VIII. Prophylaxis of bleeding in haemophilia A patients with inhibitors who have experienced a significant bleed or are at high risk of significant bleeding. *Indications in France:* This medicine is indicated: In the treatment of bleeding and in surgery interventions in inherited deficiency of factor VIII (haemophilia A), in "high responders" patients who developed an inhibitor against factor VIII. In case of failure to factor VIIa, in the treatment of bleeding and in surgery interventions in inherited deficiency of factor IX (haemophilia B), in "high responders" patients who have developed an inhibitor against factor IX. According to medical evaluation, in prophylaxis to prevent or reduce the frequency of haemorrhage in patients with very frequent bleeding episodes and haemophilia A "high responders" who developed an inhibitor directed against factor VIII or haemophilia B "high responders" who developed an inhibitor directed against factor IX, after failure by factor VIIa. In the treatment of haemorrhages and in surgical situation in patients with haemophilia acquired by anti-factor VIII auto-antibodies.	
Posology and Method of Administration	70 – 100 U/kg every other day Intravenous infusion	

Notes:
1. Country codes: Iceland (IS), Norway (NO)
2. Indication presented is that obtained from UK SmPC unless otherwise stated
3. Data collected from EMA website, Heads of Medicines Agencies MRI Product Index, ANSM website (ansm.sante.fr) and medicines.org website.

Recently the following product was also authorised: Beqvez is indicated for the treatment of severe and moderately severe haemophilia B (congenital factor IX deficiency) in adult patients without a history of factor IX inhibitors and without detectable antibodies to variant AAV serotype Rh74.

The current proposed indication for Hympavzi in haemophilia B is:

Hympavzi is indicated for 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 factor IX inhibitors.

As the indication for Hympavzi is not restricted based on the serotype, there is not full overlap in the therapeutic indications and Beqvez will not have to be considered for the significant benefit discussion. There is also incomplete overlap with Hemgenix as it is not indicated for severe patients below the age of 18 years. Hympavzi is on the other hand indicated for patients between the ages of 12-18yrs.

Recombinant factor IX products have very broad indications. The following products are considered having completely overlapping therapeutic indications with Hympavzi namely, Idelvion, ReFixia, BeneFIX, Rixubis and Alprolix.

Significant benefit

The sponsor is proposing a claim of significant benefit based on safety considerations to recombinant factor IX products and a major contribution to patient care as their formulation is a subcutaneous injection.

The sponsor came for scientific advice which they obtained from CHMP 31 January 2019. Although they had an orphan designation from 2016, they did not raise a question on significant benefit with the COMP.

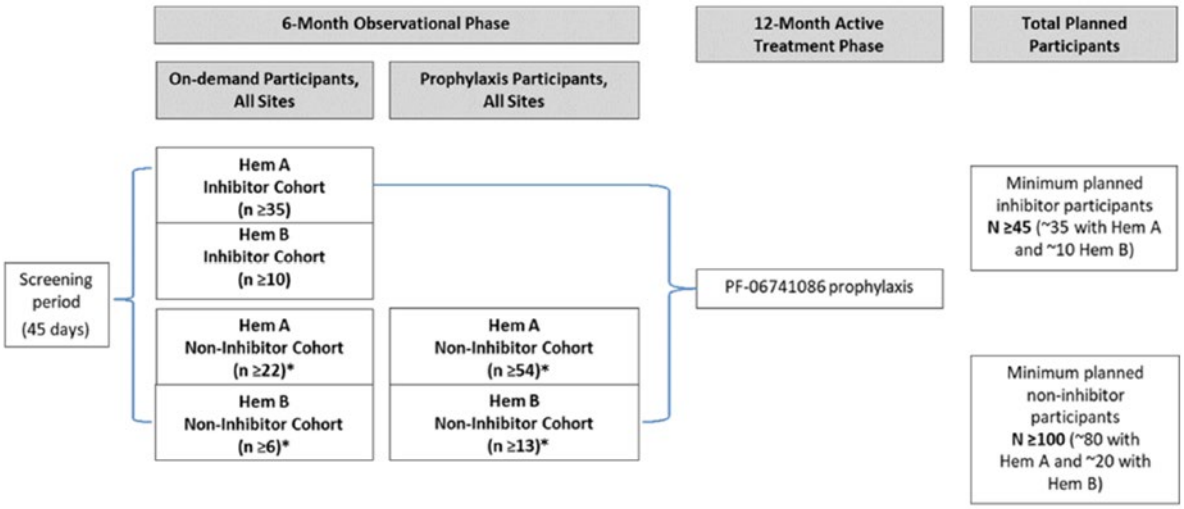
Several claims for a clinically relevant advantage are made by the sponsor to support significant benefit namely:

- that it is noninferior and superior to routine prophylactic factor-based replacement therapy and superior to on demand factor-based therapy for non-inhibitor haemophilia patients;
- in terms of efficacy in the haemophilia B adolescent (12 to < 18 years) subpopulation.
- in terms of an improved safety profile with regard to thromboembolic risk;

The main study used to support the claim for a clinically relevant advantage is study B7841005 which is their pivotal Phase III study. This was a one-way, cross-over, open-label, multicentre study planned for approximately 145 adolescent and adult participants between the ages of 12 to <75years with severe haemophilia A or moderately to severe to severe haemophilia B (defined as FVIII activity <1% or FIX activity < 2% respectively with or without inhibitor, with approximately 20% of participants as adolescents (aged between 12 to <18years old). This study was comparing treatment with the participants' prescribed factor replacement therapy or bypass therapy during an Observational Phase (OP) with a 12-month Active treatment Phase (ATP), during which participants were to receive marstacimab prophylaxis (defined as treatment by SC injection of marstacimab).

The inhibitor cohort included individuals who were receiving prior on-demand treatment (>45 participants, with at least 35 haemophilia A and 10 haemophilia B participants). The non-inhibitor cohort included >100participants with at least 80 haemophilia A and 20 haemophilia B participants.

Figure 2.



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 (e.g. 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.

Table 6. B7841005 Protocol Objectives and Endpoints

Objectives	**Endpoints**
Primary	
To demonstrate the efficacy and safety of marstacimab for routine prophylaxis in severe haemophilia A or moderately severe to severe haemophilia B (FVIII:C <1% or FIX:C ≤2%, respectively) participants 12 to <75 years of age without inhibitors.	Primary efficacy endpoint: • For the EU: non-inferiority of marstacimab versus prior prophylaxis using factor replacement as measured by the ABR of treated bleeds • For regions outside the EU: superiority of marstacimab versus prior on-demand therapy using factor replacement as measured by the ABR of treated bleeds Primary safety endpoint (without alpha control): • Adverse events (AEs) and serious adverse events (SAE)s • Incidence and severity of thrombotic events; • Immunogenicity • Incidence and severity of injection site reaction • Incidence of severe hypersensitivity and anaphylactic reactions • Incidence and severity of thrombotic microangiopathy • Disseminated intravascular coagulation/consumption coagulopathy • Changes in physical examination and vital signs • Incidence of clinically significant laboratory value abnormalities
Secondary	
Key objective: To evaluate additional efficacy of marstacimab; to evaluate the effect of marstacimab on HRQoL	Key secondary endpoints: • Common endpoints for the EU and outside the EU – Incidence of joint bleeds – Incidence of spontaneous bleeds – Incidence of target joint bleeds – Incidence of total bleeds (treated and untreated) – Physical health domain in Haem-A- QoL/Haemo-QoL • Additional key secondary endpoints for the EU – Total score in Haem-A-QoL – EQ-5D-5L Index score – EQ-5D-5L VAS score Included as key secondary endpoint for regions outside the EU is the non-inferiority of marstacimab versus prior prophylaxis using factor replacement in the ABR of treated bleeds, which is the primary endpoint for the EU.

It is noted in the maintenance report that in the EU marstacimab prophylaxis was considered non-inferior to prior prophylaxis treatment if the upper bound of the 2-sided 95% confidence interval for the difference (ATP versus OP) in ABR was less than the non-inferiority boundary of 2.5. This was measured over a period of 12 months ATP compared to routine prophylaxis during the 6 months prior to marstacimab based on the intrasubject comparison of the ABR of treated bleeds.

During the active treatment phase in the study the following therapies were prohibited unless required for emergency management of acute breakthrough bleeds in the opinion of the investigator or treating physician.

- Non-inhibitor cohort: prophylaxis treatment with FVIII or FIX replacement or any use of bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).
- Inhibitor cohort: prophylaxis, on-demand, or preventative treatment with FVIII or FIX replacement therapy. Prophylaxis treatment with bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).

The primary analysis demonstrated non-inferiority of marstacimab prophylaxis compared to routine prophylaxis of OP. The mean ABR of treated bleeds in the non-inferiority cohort was 5.08 (95% CI.40,6.77) during the active treatment period compared to 7.85 (95% CI: 5.09, 10.61) during the observational period with routine prophylaxis, resulting in an estimated ABR difference of –2.77 (95% CI:-5.37, -0.16). Since non-inferiority was demonstrated, pre-specified statistical testing for superiority was performed and demonstrated superiority with a 2-sided p-value of 0.0376.

The sponsor has also made a claim of a clinically relevant advantage regarding safety over recombinant Factor IX products but has not offered a direct comparison of serious adverse events or adverse event reporting by MEDRA listing. The sponsor has only focused on adverse events where they can show a difference between the risk of thrombotic and thromboembolic events that have been reported for recombinant Factor IX products versus none for them. The comparison of post marketing pharmacovigilance data which covers a much larger patient population than their Phase III study is unbalanced so it is difficult to establish the clinically relevant advantage here.

The current position in view of the initial non-inferiority design of the trial is to conclude that there is no difference between the sponsor's product and recombinant Factor IX products which would not support a clinically relevant advantage.

Discussion on claims for a clinically relevant advantage:

5. Marstacimab is noninferior and superior to routine prophylactic factor-based replacement therapy for non-inhibitor haemophilia B patients. It is understood that the on-demand superiority design of the trial was at the request of the FDA to reflect on practices in the US. A clinically relevant advantage based on efficacy can not be concluded upon.
6. Better efficacy in the haemophilia B adolescent (12-1<18years) subpopulation. The sponsor has made a claim of clinically relevant advantage based on fewer ABRs versus IXs in adolescents versus adults. This was shown in such a small number of patients in the Phase III trial in direct comparison to Factor IX replacement therapies that no conclusions can be drawn based on this data.
7. Improved safety over existing haemophilia B therapies as particularly evident with the occurrence of thrombosis with Factor IX and non-factor medicinal products. The sponsor has made a claim of a clinically relevant advantage regarding safety to Factor IX products indicating that they have fewer thrombotic events. They have not, however, made a comparison to all adverse events between marstacimab and these products. The selective nature of the comparison does not offer an overall picture of the safety profiles and the data available for marstacimab is limited.

The COMP concluded that the efficacy of marstacimab is at least equivalent in terms of efficacy and safety as compared with the authorised medicinal products to that of the recombinant factor IX products.

The sponsor claims regarding a major contribution to patient care based on:

- the suboptimal prophylaxis efficacy that is achieved with bypass agents in haemophilia B patients with inhibitors;
- the challenging administration route, dose schedule for prophylaxis treatment, the burden to patients and obstacles to implementation of prophylaxis that is associated with intravenously administered FIX prophylactic treatment;

The sponsor claims that FEIBA, a plasma-based product requiring administration of large volumes given IV every 2-3 days for prophylaxis, is approved for prophylaxis in haemophilia B with inhibitors in a limited number of EU countries (FEIBA Austrian SmPC, FEIBA French SmPC) (Antunes et al, 2014). As FEIBA (i.e., aPCC) contains FIX, it may trigger or worsen an allergic or anaphylactic response; for that reason, aPCC should be avoided in haemophilia B patients with inhibitors. In haemophilia A patients with inhibitors, the reduction in ABR observed during prophylaxis of haemophilia A patients with FEIBA falls short of the prophylaxis efficacy achieved with factor replacement in haemophilia A and B patients without inhibitors (Kempton & Meeks, 2014). They do not offer and direct or indirect data to their product just a statement about safety and some bridging to haemophilia A. A claim along these lines would be considered a claim for a clinical relevant advantage and not a MCPC, if this case the COMP considered that this argument was insufficient to establish either a clinically relevant advantage or a MCPC.

The sponsor has not provided any direct data between their product and the recombinant Factor IX products. There is however a broad discussion regarding the major contribution to patient care and they discuss a web-based survey of adults living with haemophilia (target n=200) and caregivers of children with haemophilia (target n=175) in the US and UK to quantify haemophilia treatment preferences.

The protocol for this survey is provided in the submission under Annex 3 titled B7841013 NON-INTERVENTIONAL STUDY PROTOCOL. This study aims to evaluate preferences of persons living with HA or HB or who care for adolescents living with HA or HB for a novel option for prophylaxis that is administered subcutaneously using a prefilled injection pen compared with other prophylaxes that use a different mode of administration. To reach the stated aim, this study has the following objectives: Primary Objectives:

- Quantify patients' and caregivers' preferences for administration, injection preparation and storage associated with routine prophylaxis for haemophilia.
- Quantify the risk patients and caregivers are willing to accept or the benefit patients and caregivers are willing to forgo in order to have their preferred administration method.

Secondary Objectives: Exploratory Objectives:

- Estimate the probability that patients and caregivers will choose different profiles representing current and future treatment options.
- Characterize unmet needs by examining patients' burden with the injection preparation and storage and identify opportunities for improving the administration and injection/infusion process of haemophilia treatments.

This was a noninterventional, cross-sectional, double-blinded study. Following best practice, a mixed methods approach was used to iteratively develop and test a preference survey for quantitative preference elicitation that addresses the study objectives.

The survey included a discrete-choice experiment (DCE) to elicit preferences for multiple features of haemophilia treatment. While data collection is still on-going an interim analysis from patients and caregivers of haemophilia A (patients n=144; caregivers n=102) and B (patients n=26; caregivers

n=22) indicates that the most important attributes to patients were dosing frequency (range: 3 fewer bleeds to 2 more bleeds). Risk of serious side effects (range: 0-5% risk during the next year of treatment), risk of developing inhibitors (range: 0-5% risk during the next year of treatment), and administration and device type (levels: intravenous infusion, subcutaneous via pre-filled pen and subcutaneous via draw up syringe) were the next most important attributes. Specifically, patients preferred SC injections to IV infusions (P<0.001). Patients numerically preferred SC injection using a Pre-filled pen (PFP) to SC injection using a vial and syringe; however, this finding was not statistically significant. Refrigeration requirements was relatively less important to patients. Requiring a second treatment for breakthrough bleeds was unimportant to patients.

Among caregivers, dosing frequency was the most important treatment feature. The next most important features were changes in the number of bleeds per year and risk of serious side effects. Risk of developing inhibitors, administration mode, and refrigeration requirements were important, but somewhat less important to caregivers. Among the administration modes, SC injections were preferred to IV infusions. Requiring an additional treatment for breakthrough bleeds was unimportant to caregivers.

Less frequent dosing was preferred by both patients and caregivers. Both patients and caregivers did not differentiate between once weekly dosing and dosing every 2-4 weeks. Patient and caregiver preferences for SC injection over IV infusions and less frequent dosing as shown in the interim analysis are consistent with the results of the study by Garcia et al. 2024 and provide further evidence that the autoinjector is a major contribution to patient care.

The study by Garcia and colleagues used an auto-injector device in the context of haemophilia treatment, which is a PFP that delivers an SC injection without mixing. Among the routes of administration included in the DCE, SC injection with a PFP was most preferred by patients when compared with SC injection with a syringe or IV infusions. Caregivers preferred SC injections to IV infusions. The auto-injector device may also enhance treatment adherence, as it reduces the burden and discomfort of administration. Moreover, the auto-injector device may facilitate home-based treatment which has the potential to improve patients' autonomy and reduce healthcare costs. These results suggest that the auto-injector device may represent a valuable option for patients and caregivers who seek a less burdensome way to deliver haemophilia treatment and, therefore, may constitute a major contribution to patient care.

The COMP agreed that a major contribution to patient care between intravenous solutions the delivery system of choice for factor IX products and subcutaneous injections has been established through the interim analysis provided in the discrete-choice experiment B7841013 NON-INTERVENTIONAL STUDY PROTOCOL.

3.4. COMP list of issues

Not applicable

3.5. COMP position

The COMP considered that it could recommend maintaining the orphan designation for Hympavzi in the treatment of haemophilia B. As this submission was in parallel with the submission for Hympavzi in haemophilia A the sponsor considered that the decision from this later submission for maintenance was linked. As the outcome for maintaining the orphan designation for Haemophilia A was not favourable the sponsor requested the orphan status to be removed for haemophilia B on the 9th of October 2024, at the same time as the request for removal of the orphan status for haemophilia A.