26 March 2026
EMADOC-1700519818-2854393
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hympavzi

International non-proprietary name: Marstacimab

Procedure No. EMA/VR/0000304590

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Term
ABR	annualized bleeding rate(s)
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
aRMM	additional risk minimization measure
AST	aspartate aminotransferase
AT	antithrombin
ATP	Active Treatment Phase
AUC	area under the concentration-time curve
AUC_{ss}	area under the concentration-time curve at steady-state
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{avg}	average observed concentration
$C_{avg,ss}$	average observed concentration at steady state
CFC	clotting factor concentrates
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
CO	Clinical Overview
COVID-19	coronavirus disease 2019
CSR	Clinical Study Report
DDI	drug-drug interaction
DIC	disseminated intravascular coagulation
DP	drug product

Abbreviation	Term
dPT	dilute prothrombin time
ECG	electrocardiogram
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5 Dimension 5 Level
EQ-VAS	EQ visual analogue scale
ER	exposure-response
EU	European Union
FDA	Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIH	first-in-human
FIX	Factor IX
FVIIa	Factor VII (activated)
FVIII	Factor VIII
FXa	Factor X activated
GCP	Good clinical practice
Haem-A-QoL	Hemophilia Quality of Life Questionnaire for Adults (≥17 years of age)
Haemo-QoL	Hemophilia Quality of Life Questionnaire for Children (12 to <17 years of age)
HJHS	Hemophilia Joint Health Score
HLT	High Level Term
HRQoL	health-related quality-of-life
IgG	immunoglobulin G
IgG1	immunoglobulin G1
ISR	injection site reaction
IV	intravenous(ly)
K1	Kunitz domain 1
K2	Kunitz domain 2
MAA	Marketing authorisation application

Abbreviation	Term
mAbs	monoclonal antibodies
mRNA	messenger RNA
N	total number, total sample size
n	number (subgroup or subpopulation)
NAb	neutralizing antibody
OD	on-demand
OLE	open-label extension
OP	Observational Phase
PD	pharmacodynamic(s)
PDCO	Paediatric Committee (Committee for Medicinal Products for Human Use [CHMP] of European Medicines Agency [EMA])
PF 1+2	prothrombin fragment 1 +2
PFP	pre-filled pen
PFS	pre-filled syringe
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PMAR	Population Modeling Analysis Report
PRO	patient-reported outcome
PT	(MedDRA) Preferred Term; prothrombin time
QoL	quality of life
QW	once weekly
rFVIIa	recombinant tissue factor-activated coagulation Factor VII
RP	routine prophylaxis
RSE	relative standard error
SAE	serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation

Abbreviation	Term
siRNA	small interfering ribonucleic acid
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
T_{max}	time of occurrence of C_{max}
TMDD	Target Mediated Drug Disposition
TNF-α	tumor necrosis factor α
ULN	upper limit of normal
V_{ss}	steady state volume of distribution
WFH	World Federation of Hemophilia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe Ma EEIG submitted to the European Medicines Agency on 10 October 2025 an application for a variation.

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of routine prophylaxis of bleeding episodes in patients 12 years of age and older with haemophilia A with factor VIII inhibitors or haemophilia B with factor IX inhibitors for HYMPAVZI, based on final results from study B7841005 and interim results from supportive study B7841007. Study B7841005 is an open-label study in adolescent and adult severe haemophilia A or moderately severe to severe haemophilia B (coagulation FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitors comparing standard treatment to PF-06741086 (marstacimab) prophylaxis. Study B7841007 is an open-label extension study to evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in severe (coagulation factor activity <1%) hemophilia A participants with or without inhibitors or moderately severe to severe hemophilia B participants (coagulation factor activity ≤2%) with or without inhibitors. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000226246 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000226246 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH received scientific advice and protocol assistance from the CHMP as follows:

Date	Reference
21 July 2016	EMEA/H/SA/3363/1/2016/I
20 July 2017	EMEA/H/SA/3363/2/2017/PA/II
26 July 2018	EMEA/H/SA/3363/2/FU/1/2018/PA/II
31 January 2019	EMEA/H/SA/3363/4/2018/II
31 January 2019	EMEA/H/SA/3363/3/2018/PA/III
19 May 2022	EMA/SA/0000086196
19 May 2022	EMA/SA/0000086197

The scientific advice and protocol assistance pertained to quality, non-clinical and clinical aspects and in relation to paediatric development of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Not applicable

PRAC Rapporteur: Marie Louise Schougaard Christiansen

Timetable	Actual dates
Submission date	10 October 2025
Start of procedure:	1 November 2025
CHMP Rapporteur's preliminary assessment report circulated on:	19 December 2025
PRAC Rapporteur's preliminary assessment report circulated on:	5 January 2026
PRAC outcome:	15 January 2026
CHMP comments	19 January 2026
Updated CHMP AR	21 January 2026
Request for supplementary information adopted by the CHMP on:	29 January 2026
MAH responses submitted to the CHMP on:	24 February 2026
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 March 2026
CHMP comments	16 March 2026
Updated CHMP AR	19 March 2026
CHMP opinion:	26 March 2026
The CHMP adopted a report on similarity of Hympavzi with Roctavian, Altuvoct, Idelvion, Alprolix and Hemgenix on date (Appendix 1)	26 March 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Haemophilia A and B are bleeding disorders caused by a deficiency of coagulation factor VIII (FVIII) or coagulation factor IX (FIX), respectively, each of which is a key component of the intrinsic pathway. Patients with haemophilia have some ability to initiate coagulation through their extrinsic pathway; however, this is not sufficient to control bleeding episodes because the extrinsic pathway is rapidly shut down by Tissue Factor Pathway Inhibitor (TFPI). *In vitro* studies indicate that continued bleeding in haemophilia requires not only the absence of FVIII or FIX, but also the presence of TFPI.

Treatment of haemophilia A or B is primarily achieved through replacement of missing FVIII or FIX, respectively, via either episodic or prophylactic infusions of coagulation factor concentrate. A substantial number of patients develop neutralising antibodies (Nabs) (inhibitors) to the administered factor products, leading to important challenges due to the severity and frequency of their bleeding episodes and difficulties in managing them.

Claimed 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 h~~Haemophilia A (congenital factor VIII deficiency~~, FVIII < 1%~~):
  - ~~o~~ ~~w~~Without factor VIII inhibitors **who have severe disease (FVIII < 1%)**, ~~or~~
  - **With factor VIII inhibitors**
- ~~severe h~~Haemophilia B (congenital factor IX deficiency~~, FIX < 1%~~):
  - W~~w~~ithout factor IX inhibitors **who have severe disease** (**FIX < 1%).**
  - **With factor IX inhibitors**

Epidemiology

Globally, haemophilia A occurs at a rate of approximately 17.1 cases per 100,000 males. The estimated average incidence rate was 1 in 5,617 male births for haemophilia A in the US in a study using the haemophilia treatment centres (HTC) network, with an incidence rate at birth of 17.9 per 100,000 male births. According to the US Centres for Disease Control and Prevention (CDC), approximately 400 boys are born with haemophilia A each year in the US. The prevalence at birth was 24.6 cases per 100,000 male births for all severities of haemophilia A and 9.5 cases for severe haemophilia based on data from the 3 most established registries (Canada, France, and the United Kingdom).

Haemophilia B occurs globally at an annual rate of approximately 1 in 30,000 (3.33 per 100,000) male live births and the incidence rate in the US is 5.3 per 100,000 male births. While the CDC does not report an estimate for how many boys are born annually with haemophilia B, haemophilia B is estimated to be about 3.4 times less common than haemophilia A. The prevalence at birth was 5 cases per 100,000 male births for all severities of haemophilia B and 1.5 cases for severe haemophilia B in

an international study including Australia, Canada, France, Italy, New Zealand, and the United Kingdom.

Up to 32% of patients with severe haemophilia A, and up to 5% of patients with severe haemophilia B develop NAbs (inhibitors) to the administered factor products.

Aetiology and pathogenesis

The genes encoding FVIII and FIX are on the long arm of the X chromosome. Haemophilia A and B are the only hereditary clotting diseases inherited in a sex-linked recessive pattern.

The genetic mutations cause a quantitative decrease in protein expression, a qualitative decrease in protein activity, or both. Approximately 5% to 10% of patients with haemophilia A and 40% to 50% of patients with haemophilia B make a dysfunctional protein, which results in decreased protein activity without a quantitative decrease. More than 1000 mutations in either the factor VIII or factor IX genes have been identified to cause clinical haemophilia. There is a high rate of spontaneous mutation (approximately one-third of cases) such that even in the absence of a family history, haemophilia should be suspected in a newborn with bleeding and a prolongation in the Partial Thromboplastin Time (PTT).

Management

Treatment of haemophilia A or B in patients without inhibitors is primarily achieved through replacement of missing FVIII or FIX, respectively. Due to the relatively short half-lives of FVIII and FIX, effective prophylactic treatment in patients without inhibitors requires IV administration up to 1 to 4 times each week for FVIII products, and twice a week to twice a month for FIX products. Limitations with current haemophilia standard of care treatment include the burden associated with factor prophylaxis treatment, such as challenges with maintaining IV access. Gene therapies for haemophilia A (Roctavian) and B (Hemgenix) have recently been approved in several regions, offering long-term factor expression after a single infusion. However, these treatments are not indicated for patients with FVIII or FIX inhibitors and are currently limited to adults and their durability varies between individuals.

Inhibitors are associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges. Children and adults with inhibitors have higher rates of hospitalisation, greater treatment costs, and higher mortality rates than those without inhibitors. These patients can undertake immune tolerance induction to eliminate the inhibitor, and/or alternative means of haemostatic treatment which include the bypassing agents which function by circumventing the need for FVIII or FIX to promote thrombin generation, including eptacog alfa (activated recombinant coagulation FVII, rFVIIa, NovoSeven RT) or aPCC (FEIBA), which activate coagulation through the extrinsic and/or the final common pathway. FEIBA is a plasma-derived product requiring weight-based administration, by IV infusion of large volumes every 2 days for prophylactic use. Of note, aPCC contains FIX, and may trigger or worsen an allergic or anaphylactic response, therefore it should be avoided in haemophilia B patients. Thrombotic complications, though rare, are a concern, when high doses or combinations are used.

Hemlibra (emicizumab), a bi-specific antibody that bridges activated coagulation factor IXa and factor X (to replace the function of missing activated FVIII), was approved in the EU for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with and without inhibitors. Hemlibra is administered SC and is currently approved at frequencies ranging from once

weekly to once every 4 weeks. Hemlibra has been authorised for the treatment of haemophilia A patients.

Alhemo (concizumab) is a TFPI antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and paediatric patients 12 years of age and older with haemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors or haemophilia B (congenital FIX deficiency) with or without FIX inhibitors. Alhemo is approved for once-daily SC administration. Alhemo uses weight-based dosing and requires drug monitoring and dose optimisation.

2.1.2. About the product

Marstacimab is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI), the primary inhibitor of the extrinsic coagulation cascade. TFPI initially binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2). Thus, neutralising the activity of TFPI may serve to enhance the extrinsic pathway and reduce or eliminate the need for replacement FVIII or FIX.

Marstacimab is currently approved in the EU for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35kg, 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.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received the following scientific advice and protocol assistance:

Date	Reference
21 July 2016	EMEA/H/SA/3363/1/2016/I
20 July 2017	EMEA/H/SA/3363/2/2017/PA/II
26 July 2018	EMEA/H/SA/3363/2/FU/1/2018/PA/II
31 January 2019	EMEA/H/SA/3363/4/2018/II
31 January 2019	EMEA/H/SA/3363/3/2018/PA/III
19 May 2022	EMA/SA/0000086196
19 May 2022	EMA/SA/0000086197

The scientific advice and protocol assistance pertained to the following quality, non-clinical, and clinical aspects.

EMEA/H/SA/3363/1/2016/I – Non-clinical development

- The need for a chronic toxicity study in monkeys; the proposed juvenile toxicity studies; the proposed combination pharmacology study with PF-06741086 and eptacog alfa; the need for a fertility study in female animals and embryo foetal developmental toxicity studies; the proposed waiver for carcinogenicity studies.

EMEA/H/SA/3363/2/2017/PA/II – Clinical development

- The proposed clinical development plan to characterise the PK, PD, safety, immunogenicity and efficacy of PF-06741086 for prophylaxis treatment of young children, adolescent, and adult individuals with haemophilia A (with/without inhibitors); characterisation of PD and PK of PF-06741086 across the anticipated range of ages to be treated; the adequacy of the proposed safety data package to characterise the overall safety of routine prophylactic treatment with PF-06741086; the proposed plan to characterise thrombotic safety of PF-06741086 in haemophilia patients with inhibitors during concomitant treatment with eptacog alfa; the proposed characterisation of immunogenicity; the approach to flat clinical dosing for PF-06741086; the proposed primary endpoint for prophylaxis efficacy to show an effect in subjects receiving routine prophylaxis treatment with PF-06741086 compared to on-demand treatment; the proposed phase 3 programme to support the initial MAA for individuals aged 12 to <65 years with and without inhibitors; the proposed paediatric development and staggered approach for inclusion of paediatric patients in clinical trials; the proposed justification to not study paediatric patients <2 years with inhibitors and without inhibitors; the proposed timing of conducting the paediatric study and strategy for MAA; the need for a separate clinical study in paediatric patients ages 2 to <12 years without inhibitors; the proposed data packages to support the initial indication of prophylaxis in adolescent and adult patients with haemophilia A (and B) patients with inhibitors, and subsequent extensions of the indication to include a) adolescent and adult haemophilia A (and B) patients without inhibitors and b) young paediatric haemophilia A (and B) patients with inhibitors (and without inhibitors if supported by analysis of available data).

EMEA/H/SA/3363/2/FU/1/2018/PA/II – Clinical development

- Usability evaluation of the prefilled pen; clinical bridging between delivery presentations (prefilled syringe to prefilled pen).

EMEA/H/SA/3363/4/2018/II – Clinical development

- The design of the pivotal Phase 3 study B7841005 in haemophilia A or B subjects aged 12 years and older with and without inhibitors and, in particular, the staged enrolment of non-inhibitor patients on prior prophylaxis, dosing regimen, primary endpoint, and statistical analysis; the strategy to submit an initial MAA in haemophilia A or B inhibitor patients at the time of an interim analysis; adequacy of the overall clinical development plan to characterise the safety, tolerability, efficacy, PK, PD, and immunogenicity of PF-06741086; the proposed paediatric development strategy.

EMEA/H/SA/3363/3/2018/PA/III – Quality, Non-clinical and Clinical development

- The proposed potency assay.
- The design of the proposed combination pharmacology study in rats with PF 06741086 and FEIBA; the proposed waiver for carcinogenicity studies; appropriateness of the overall non-clinical development programme for MAA.
- The same clinical questions as for procedure EMEA/H/SA/3363/3/2018/PA/III.

EMA/SA/0000086196 - Clinical development

- Proposal to file an initial MAA in patients with haemophilia A without inhibitors, upon completion of 12 months of active dosing for participants in the non-inhibitor cohorts, in particular adequacy of the safety analyses, and inclusion of adolescent patients aged 12 and above.

EMA/SA/0000086197 - Clinical development

- Proposal to file an initial MAA in patients with haemophilia B without inhibitors, upon completion of 12 months of active dosing for participants in the non-inhibitor cohorts, in particular adequacy of the safety analyses, and inclusion of adolescent patients aged 12 and above.

The guideline on the clinical requirements for non-replacement therapy in haemophilia A and B (EMA/CHMP/BPWP/518080/2024) is applicable for this development programme.

The applicant/MAH has generally followed the recommendations received in the protocol assistance/scientific advice procedures and laid out in the draft guideline, but some issues had to be justified during the initial MAA procedure.

Hympavzi (marstacimab) was designated as an orphan medicinal product for the following conditions: treatment of haemophilia A and treatment of haemophilia B. The orphan designation was withdrawn by the applicant on 9 October 2024.

2.1.4. General comments on compliance with GLP and GCP

Nonclinical combination studies with marstacimab (already submitted with the initial MAA) were not conducted according to GLP. However, clinical studies are already available, which recruited haemophilia patients with inhibitors (B7841005, B7841008, B7841007), and bypassing agents (e.g., aPCC, rFVIIa) were used for treatment of breakthrough bleeds. The non-clinical data are thus regarded of supportive value only.

The clinical trials were performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

2.2.1. Introduction

One new non-clinical *in vitro* study (study 042724) was submitted to investigate the combination of marstacimab and emicizumab.

Furthermore, new information on previously submitted (and assessed) *in vitro* and *in vivo* studies on concomitant / bypass therapy was included in the SmPC sections 4.5 and 5.3. This information refers to the effects of combined, repeat-dose administration of marstacimab and available bypass treatments (i.e., NovoSeven-RT [rFVIIa], FEIBA, or Byclot).

2.2.2. Pharmacology

Data from study 042724 revealed that *in vitro*, the combination of marstacimab and emicizumab increased thrombin generation compared to marstacimab treatment alone in human haemophilia A plasma with or without inhibitor, without exceeding peak thrombin levels achieved in non-haemophilic plasma treated with marstacimab alone and were within the range in studies reported for non-hemophilic normal plasma (Pittman *et al,* 2022; Dargaud *et al,* 2005). These *in vitro* TGA results are reported to be potentially supportive of sequential administration of emicizumab (Hemlibra) and marstacimab in haemophilia A patients switching between therapies.
Previous data on combination of treatment showed that *in vitro* studies in haemophilia A and B plasma with inhibitors, evaluating marstacimab in combination with rFVIIa (NovoSeven RT), or aPCC (FEIBA), or FVIIa/FX (Byclot), resulted in higher peak thrombin concentration compared to addition of either alone. However, thrombin generation in these studies did not exceed levels observed in non-haemophilic plasma dosed with marstacimab alone, and in some cases were within the range in studies reported for non-haemophilic normal plasma.

In non-haemophilic male rats, treatment resulted in an increased incidence and/or severity of acute thrombi/emboli in the lung and injection site with NovoSeven-RT co-administration, and higher mean thrombin-antithrombin complexes and mean platelet volume with FEIBA co-administration, relative to controls. Effects of co-administration of marstacimab and Byclot were similar to those observed with Byclot alone and limited to effects on coagulation parameters. Marstacimab exposures were not affected by co-administration of NovoSeven-RT (rFVIIa), FEIBA, or Byclot, according to summaries provided by the MAH.

Primary pharmacodynamic studies

In Vitro Pharmacodynamics

New study:

In Vitro Characterisation of Marstacimab Activity in Human Haemophilia Plasma in Combination with Emicizumab (Hemlibra) in a TGA Assay (Study 042724)

Haemophilia A patients with or without inhibitor who are on emicizumab (Hemlibra) may switch to treatment with marstacimab. The potential additive effect of marstacimab and emicizumab added *in vitro* to haemophilia A plasma with and without inhibitor was assessed using a thrombin generation assay. For combination studies, emicizumab concentration (100, 50 and 25 µg/mL) were chosen to approximate the range of steady state plasma concentrations after a 6 mg/kg once monthly dose. The concentration of marstacimab (80, 16, and 4 µg/mL) were chosen to approximate the range of steady state concentrations observed across the Phase 1, 2 and 3 studies.

Marstacimab and emicizumab improved thrombin generation in all the plasmas. Non-haemophilic plasma, with the full complement of coagulation factors, alone or spiked with marstacimab was also analysed. Consistent with the TFPI inhibitory activity of marstacimab, the addition of marstacimab to non-haemophilic human platelet-poor plasma, increased peak thrombin and decreased the lag time, without excessive thrombin generation (Pittman *et al,* 2022).

The combination of marstacimab and emicizumab increased thrombin generation compared to that of marstacimab treatment alone. However, the peak thrombin levels achieved by the combination of marstacimab and emicizumab in haemophilia A plasma samples did not exceed those achieved in non-haemophilic plasma treated with marstacimab and were within the range in studies reported for non-haemophilic normal plasma (Dargaud *et al,* 2005). These in vitro TGA results are potentially supportive of sequential administration of emicizumab and marstacimab in haemophilia A patients switching between therapies.

Summary of previously assessed *in vitro* data referred to in the SmPC:

Previous data on combination of treatment showed that *in vitro* studies in haemophilia A and B plasma with inhibitors, evaluating marstacimab in combination with rFVIIa (NovoSeven RT), or aPCC (FEIBA), or FVIIa/FX (Byclot), resulted in higher peak thrombin concentration compared to addition of either alone. However, thrombin generation in these studies did not exceed levels observed in non-haemophilic plasma dosed with marstacimab alone, and in some cases were within the range in studies reported for non-haemophilic normal plasma.

In Vivo Pharmacodynamics

Summary of previously assessed *in vivo* combination studies referred to in the SmPC:

Prior to the co-administration of the bypass agents in clinical studies, combination pharmacology studies in rats with marstacimab and NovoSeven-RT, FEIBA, or Byclot were conducted to investigate the cumulative pharmacodynamics and potential additive effects of co-administration of these treatments. Rats were selected as the species for the combination pharmacology studies since the rat is a pharmacologically relevant species that was also used in the toxicity studies.

Study designs for NovoSeven-RT and FEIBA were reviewed by the FDA and CHMP and were considered acceptable (NovoSeven-RT: FDA Written Response dated 11 May 2016 and FDA response to Pfizer Clarification Request dated 01 September 2016; CHMP Scientific Advice, EMA/H/SA/3363/1/2016/I, 21 July 2016; FEIBA: IND 126734 Written Responses dated 29 October 2018, CHMP Protocol Assistance, EMA/H/SA/3363/3/2018/PA/III, 31 January 2019).

The combination pharmacology study with marstacimab and Byclot was conducted based on discussion with PMDA (End of Phase 2 Study Consultation Notification No. 0117005, 17 January 2019).

Concomitant administration of marstacimab and NovoSeven RT did not alter systemic exposures (Cmax and AUCt) of each other. Enhanced efficacy by co-administration, reflected by an increased incidence and /or severity of minimal to mild, acute thrombi/emboli in the lung and injection site (tail), was only seen in the NovoSeven RT high dose group. Combined treatment of marstacimab and FEIBA was investigated and did not reveal any changes in systemic exposure (Cmax and AUC48) of marstacimab. Furthermore, combined treatment of marstacimab and FEIBA showed similar results as reported for FEIBA alone (e.g. increase in Thrombin-antithrombin (TAT) concentrations and activated partial thromboplastin time and decrease in prothrombin time, correlating with clinical signs as well as macroscopic and microscopic observations), but with an additive increase in TAT concentrations, slightly higher mean platelet volume values, and no increased incidence for test article-related thrombi/emboli in the lung. Combined treatment of subcutaneously administered marstacimab and intravenously dosed Byclot was assessed, where an increase in thrombin:antithrombin-complex concentrations was observed in rats after co-treatment, whereas marstacimab alone did not result in any test-article-related effects. Overall, treatment of rats with marstacimab alone led to no test-article related changes in Prothrombin time (PT); activated partial thromboplastin time (aPTT; as expected) and Thrombin-antithrombin complexes (TAT) were elevated in the combination study with Byclot; higher TAT values (about 2x of control) in the FEIBA study; and no changes in PT in the Novoseven combination study, indicating only low pharmacodynamic response to marstacimab in this animal model.

The combination studies of marstacimab with NovoSeven RT (study 16MA086), FEIBA (study 19GR258) or Byclot (study 22GR075) in male Wistar Han rats were mainly conducted to support the inclusion of patients with inhibitors in clinical studies.

Table 1: Summary of Key Pharmacologic Properties of marstacimab (newly submitted data outlined in red)

Study	Assay	Pharmacodynamic Activity
In vitro: Study 072904	Surface Plasmon Resonance Binding to recombinant Human TFPI K1K2 Mouse TFPI K1K2 Rat TFPI K1K2 Rabbit TFPI K1K2 Cynomolgus Monkey TFPI K1K2	Binding Affinity (K_D) 3.7 nM ± 0.28 0.575 nM ± 0.05 1.57 nM ± 0.04 4.25 nM ± 0.05 1.22 nM ± 0.03
In vitro Study 121926	Surface Plasmon Resonance Binding affinity to hTFPI K1, K2, and K1K2	Binding Affinity (K_D) No binding (K1), 2.63±0.08 nM (K2) and 7.91± 0.33 nM (K1K2), respectively
In vitro: Study 085202	Reversal of FXa Enzyme Inhibition Assays Factor Xa Activity Factor VIIa/Tissue Factor/Factor Xa Activity	 EC_{50} = 1312 ng/mL EC_{50} = 1985 ng/mL
In vitro: Study 142056	Human Whole Blood Assays Dose-response Citrated Non-hemophilic TEG parameters R value clotting time K value clot formation time	 Decreased Decreased
In vitro: Study 123404 In vitro: Study 123404 In vitro: Study 123404	Dose-Response dPT Citrated Platelet Poor Non-Hemophilic Plasma Human Rabbit Cynomolgus Monkey Dose-Response aPTT Citrated Platelet Poor Non-Hemophilic Pooled Plasma Dose-Response TGA Citrated Platelet Poor Non-Hemophilic Pooled Plasma	dPT EC_{50} = 406 ng/mL EC_{50} = 629 ng/mL EC_{50} = 273 ng/mL No response Peak thrombin increased; lag time decreased

In vitro: Study 135025	Dose-Response dPT Citrated Platelet Poor Hemophilic Pooled Plasma Hemophilia A, Hemophilia B and Hemophilia A (BU = 176)	dPT Similar EC_{50} values
In vitro: Study 135025 In vitro: Study 135025	Dose-Response aPTT Citrated Platelet Poor Hemophilic Pooled Plasma Hemophilia A, Hemophilia B and Hemophilia A (BU = 176) Dose-Response TGA Citrated Platelet Poor Human Hemophilic Pooled Plasma Hemophilia A, Hemophilia B and Hemophilia A (BU = 176)	 Minimal response Peak thrombin increased; lag time decreased
In vitro: Study 122443	Dose-Response TGA Citrated Platelet Poor Human Hemophilic Plasma Hemophilia A, Hemophilia B and Hemophilia A with inhibitors (BU = 3 - 1261) Combination with 2 µg/mL rFVIIa marstacimab dosed Non-Hemophilic Pooled Plasma	 Peak thrombin increased; lag time decreased Did not exceed the level observed in non-hemophilic plasma dosed alone
In vitro: Study 045123	Dose-Response TGA Citrated Platelet Poor Human Haemophilic Plasma Haemophilia A and Haemophilia B with inhibitors (BU = 14 - 160) Combination with 1 U/mL FEIBA (aPCC) Marstacimab dosed Non-Hemophilic Pooled Plasma	Peak thrombin increased; lag time decreased No additive decrease observed in the lag time with the combination of marstacimab and aPCC (FEIBA), Higher peak thrombin concentration compared to the addition of either alone, but was within the range in studies reported for non-hemophilic normal plasma
In vitro: Study 103228	Characterization of marstacimab activity (thrombin generation): Byclot Alone (FVIIa/FX ratios 0.25/2.5 to 8/80 µg/mL) in Hemophilia A or B inhibitor plasma Marstacimab alone (16 µg/mL) in Hemophilia A or B inhibitor plasma or non-hemophilic plasma Combination: marstacimab (16 µg/mL) + Byclot FVIIa/FX (0.5/5 – 2/20 µg/mL) in Hemophilia A or B inhibitor plasma	A decrease in the lag time was observed with both marstacimab (16 µg/mL) and Byclot (FVIIa /FX at 2/20 or 1/10 or 0.5/5 µg/mL) alone in hemophilia plasma. No additive decrease in the lag time with marstacimab and Byclot in combination was observed. Addition to hemophilia plasmas with an inhibitor increased thrombin generation, including higher peak thrombin concentration compared to the addition of either agent alone that was within the range reported in studies for non-hemophilic normal plasma.
In vitro: Study 042724	Characterization of marstacimab activity (thrombin generation) in combination with emicizumab: **Emicizumab** (25, 50, or 100 µg/mL) **PF-06741086** (4, 16, or 80 µg/mL) **aPCC (FEIBA®)** 1 U/mL **rFVIIa** 2 µg/mL **Hemophilia A plasma lots:** 7491 (0 BU); 6100 (1 BU); 7451(2.4 BU);	**Effects of treatment alone compared to untreated hemophilia plasma:** Marstacimab • increased thrombin generation in all plasmas, including higher peak thrombin concentration • shortened lag time Emicizumab • improved thrombin generation in all the plasmas • small effect on lag time **Combination of marstacimab and emicizumab:**

	3725 (128 BU); 6091 (88 BU)	• increased thrombin generation compared to that of marstacimab treatment alone • achieved peak thrombin concentration within the range reported in studies for normal non-hemophilic plasma. • supports sequential administration of emicizumab and marstacimab in hemophilia A patients switching between therapies. **Combination of emicizumab and aPCC** • synergistic increase in thrombin generation parameters • emicizumab (100 µg/mL) and 1 U/mL of aPCC increased the peak thrombin ~10-fold compared to emicizumab alone **Combination of marstacimab, emicizumab, and rFVIIa** • dose dependent increase in thrombin generation vs marstacimab combined with emicizumab • shortened lag time with rFVIIa alone
In vivo Study 135244	Hemophilic Mouse Tail Clip Injury Administration prior to injury Lowest dose with significant effect in Hem A Duration of effect in Hemophilia A	1 mg/kg, 189 hours
In vivo Study 135244	Mouse IVM Laser Induced Injury, Hemophilia A Quantitation of platelet and fibrin accumulation Administration prior to injury Duration	Increased platelet and fibrin accumulation 168 hours
In vivo Study 121321	Hemophilic Mouse Tail Clip Injury Administration prior to injury Duration of effect Hemophilia B	At least 72 hours
In vivo Study 121321	Hemophilic Mouse Tail Clip Injury Administration up to 2 minutes post injury Hemophilia A	Restored hemostasis
In vivo Study 121321	Mouse IVM Laser Induced Injury Hemophilia A Quantitation of platelet and fibrin accumulation Administration post injury	Increased platelet and fibrin accumulation
In vivo 16MA086	10-Day Intravenous Investigative Study of Marstacimab and Novoseven®RT in Male Wistar Han Rats	Increased incidence and/or severity of microscopic minimal to mild, acute thrombi/emboli in lung and injection site (tail) with combined administration of marstacimab (50 mg/kg) and NovoSeven® RT (3 mg/kg). Systemic exposures characterized by C_{max} and AUC_t for marstacimab and NovoSeven RT were not affected by combined test article administration.
In vivo 19GR258	10-Day Subcutaneous (Once Weekly) or 3-Day (Twice Daily) Intravenous Investigative Study of Marstacimab or Factor VIII Inhibitor Bypassing Activity (FEIBA) in Male Wistar Han Rats	Combined administration of FEIBA and marstacimab (30 mg/kg/day) resulted in similar clinical observations, clinical pathology differences, macroscopic and microscopic findings compared with FEIBA (≥10 [5 BID] U/kg/day) alone, except for higher

Study	Assay	Pharmacodynamic Activity
		means for thrombin-antithrombin complexes and mean platelet volume at all FEIBA combined doses. Mean systemic exposure of marstacimab characterized by AUC_{48} was similar in all dose groups (marstacimab alone or in combination with FEIBA).
In vivo 22GR075	10-Day Investigative Study of Marstacimab and Byclot® in Male Rats	Co-administration of marstacimab (30 mg/kg/day) and Byclot® resulted in changes in coagulation parameters including prothrombin time, activated partial thromboplastin time, and thrombin:antithrombin complexes which were similar to changes observed with Byclot® alone. Systemic exposure of marstacimab was not affected by Byclot® co-administration.
In Vivo 8299672	PD effect of marstacimab in male cynomolgus monkey plasma demonstrated by dPT	Decrease in dPT: stable decrease in dPT clotting time from 24 to 240 hours following a single IV (1 mg/kg) or SC (3 or 10 mg/kg) dose of marstacimab (2 animals per group).

Antibody molecular weight = 150 kilodaltons.

Pharmacodynamic drug interactions

According to summaries provided by the MAH, *in vitro* and *in vivo* pharmacodynamic drug interaction studies with marstacimab and available bypass agents (e.g., NovoSeven-RT, FEIBA, or Byclot) support the concomitant use of marstacimab with these products. Non-clinical pharmacology studies in rats with normal FVIII and FIX levels support the concomitant use of marstacimab and clinical doses of rFVIIa (90 µg/kg) or FEIBA (100 U/kg) for the treatment of breakthrough bleeds with marstacimab in patients with haemophilia A or B with inhibitors.

2.2.3. Ecotoxicity/environmental risk assessment

The active substance is a monoclonal antibody (i.e. of protein structure), susceptible to physical and biological degradation. Therefore, marstacimab is not expected to pose a risk to the environment.

2.2.4. Discussion on non-clinical aspects

In the newly submitted non-clinical *in vitro* study 042474, marstacimab activity with or without emicizumab was evaluated using a thrombin combination assay. Haemophilia A patients on emicizumab may transition to marstacimab therapy, and their combined effect was evaluated *in vitro*. Emicizumab and marstacimab concentrations were selected to reflect clinically relevant steady-state levels from respective dosing regimens and trials. Both agents alone improved thrombin generation in haemophilia A plasma, and marstacimab alone enhanced thrombin generation in non-haemophilic plasma without causing excessive coagulation compared to levels reached in normal healthy plasma. The combination of marstacimab and emicizumab further increased thrombin generation in human haemophilia A plasma with or without inhibitor compared to marstacimab alone, but peak levels remained within the normal range observed in non-haemophilic plasma and were within the range in studies reported for non-haemophilic normal plasma. These *in vitro* findings are supportive of sequential administration of emicizumab and marstacimab being safe and effective for patients

switching therapies. However, nonclinical data may not serve as sole evidence to support any claims regarding switching therapies. *In vitro* and *in vivo* pharmacodynamic drug interaction studies with marstacimab and available bypass agents (e.g., NovoSeven-RT, FEIBA, or Byclot) to support the concomitant use of marstacimab with these products, were already submitted and assessed during the initial MAA of marstacimab. Briefly summarised, a minimal additive effect in peak thrombin generation was observed with the combination of marstacimab and rFVIIa (NovoSeven-RT) in severe haemophilia A and B plasma. In haemophilia A and B plasma with inhibitors, the combination of marstacimab and aPCC (FEIBA) resulted in increased peak thrombin concentration compared to either alone. The addition of marstacimab in combination with Byclot to haemophilia plasma with inhibitor, compared to the addition of either agent alone, increased thrombin generation, including higher peak thrombin concentration. However, all the observed increases in either combination did not exceed the range of levels observed in non-haemophilic plasma dosed with marstacimab alone.

At the time of the initial assessment it was noted by the assessors that '*the intended clinical indication of marstacimab* (at that time) *is prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors, or severe haemophilia without factor IX inhibitors*.' Thus, although the initial assessment of these nonclinical studies did not reveal any severe adverse effects (which is still valid at this time of the application for EoI), the clinical relevance of these data has changed. The combination studies of marstacimab with NovoSeven RT (study 16MA086), FEIBA (study 19GR258) or Byclot (study 22GR075) in male Wistar Han rats were mainly conducted to support the inclusion of patients with inhibitors in clinical studies.

In the available clinical studies, which recruited haemophilia patients with inhibitors (B7841005, B7841008, B7841007), bypassing agents (e.g., aPCC, rFVIIa) were used for treatment of breakthrough bleeds. No thromboembolic events were reported so far in these patients. Please refer to the clinical safety section of the assessment report for more information.

Co-administration of marstacimab (50 mg/kg) and bypass agents in non-haemophilic rats were well tolerated up to 0.8 mg/kg rFVIIa. Increased incidence or severity of acute thrombi / emboli in the lung and injection site were observed only at high doses of rFVIIa of 3 mg/kg (compared to intended 90 µg/kg in haemophilia patients). 30 mg/kg marstacimab combined with aPCC (10-100 U/kg/day) resulted in higher mean thrombin-antithrombin complexes and mean platelet volume than observed for aPCC alone, however no clinically relevant adversities were identified.

Respective paragraphs regarding these data were added to the sections 4.5 and 5.3 of the SmPC. In addition, updates to the warning in section 4.4 with regards to thromboembolic events and the guidance on treating breakthrough bleeds were included (please see clinical safety section).

2.2.5. Conclusion on the non-clinical aspects

Taken together, the nonclinical data submitted support the clinical data on the extension of indication proposed by the MAH to include haemophilia patients with inhibitors. The relevant nonclinical data was accordingly depicted in the SmPC under 4.5 and 5.3. In addition, updates to the warning in section 4.4 were implemented with regards to thromboembolic events and the guidance on treating breakthrough bleeds (please see clinical safety section).

The active substance is a monoclonal antibody (i.e. of protein structure), susceptible to physical and biological degradation. Therefore, marstacimab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Clinical studies Included in the marstacimab Clinical Development Program

Study	Description	Population	N Treated (Active/ Placebo)	Dose(s) / Frequency	Duration	Age (Years)	Study Status	Included in Type II Variation
B7841001	Phase 1 FIH Single dose	Healthy participants	32/9	Multiple/ Single dose	Single dose	≥18 to ≤55	Completed	No
B7841002	Phase 1b/2 multiple dose proof of concept	Severe haemophilia A & B	26/0 Non-inhibitor Cohort: 19 Inhibitor Cohort: 7	150, 300, 450 mg/ QW	3 months	≥18 to <65	Completed	No
B7841003	Phase 2 OLE of Study B7841002	Severe haemophilia A & B	20/0 Non-inhibitor Cohort: 13 Inhibitor Cohort: 7	150, 300 mg/QW	Up to 12 months (in addition to 3 months exposure in Study B7841002)	≥18 to <75	Completed	No
B7841005	Phase 3 Pivotal	Severe haemophilia A & moderately severe to severe haemophilia B	167/0 Non-inhibitor Cohort: 116 Inhibitor Cohort: 51	300 mg SC for initial loading dose followed by 150 mg/QW[a]	12 months	≥12 to <75	Completed	Yes (Inhibitor Cohort, ≥12 years)
B7841007	Phase 3 OLE of Parent Studies, Study B7841005 and Study B7841008	Severe haemophilia A & moderately severe to severe haemophilia B	As of the 30 May 2025 data cutoff: Total: 207/0 Non-inhibitor Cohort (from Study B7841005): 107 Inhibitor Cohort (from Study B7841005): 47	150 mg SC for initial loading dose followed by 75 mg/QW (for ≥6 to <12 years)[b] 300 mg SC for initial loading dose followed by 150 mg/QW (for ≥12 years)[a]	Up to approximately 43 months at the time of data cutoff (in addition to 12 months exposure in parent study)	≥6 to <75	Ongoing; Data cutoff: 30 May 2025	Yes (All available data from participants rolling over from Study B7841005 Inhibitor Cohort, ≥12 years; All available data from participants rolling over from B7841005 Non-inhibitor Cohort ≥12 years;

Study	Description	Population	N Treated (Active/ Placebo)	Dose(s) / Frequency	Duration	Age (Years)	Study Status	Included in Type II Variation
			Non-inhibitor Cohort (from Study B7841008): 32 Inhibitor Cohort (from Study B7841008): 21					Relevant safety data from participants rolling over from Study B7841008 Non-inhibitor and Inhibitor Cohorts, ≥6 to <18 years)
B7841007 Substudy	PFP Substudy of Study B7841007 to evaluate use of the PFP	Severe haemophilia A & moderately severe to severe hemophilia B	23 participants who enrolled in the B7841007 main study	150 mg/QW[a]	Up to 6 weeks (up to 6 consecutive weekly doses)	≥12 to <75	Completed	No
B7841008	Phase 3 pediatric	Severe haemophilia A & moderately severe to severe haemophilia B	As of the 26 May 2025 relevant safety data cutoff: Total: 92/0 ≥6 to <12 years: 68 Non-inhibitor Cohort: 52 Inhibitor Cohort: 16 ≥12 to <18 years: 24 Non-inhibitor Cohort: 15 Inhibitor Cohort: 9	To be determined for <6 years 150 mg SC for initial loading dose followed by 75 mg/QW (for ≥6 to <12 years)[b] 300 mg SC for initial loading dose followed by 150 mg/QW for ≥12 to <18 years[a]	Up to 12 months	≥1 to <18	Ongoing; Relevant safety data cutoff: 26 May 2025	Yes (Relevant safety data from Non-inhibitor and Inhibitor Cohorts, ≥6 to <18 years)
B7841009	Phase 1 Bioequivalence	Healthy participants	22/0	300 mg/Single dose	Up to 4 doses given over approximately 2 months	≥18 to ≤55	Terminated early; study objectives met	No
B7841010	Phase 1 single dose PK (Chinese participants)	Severe haemophilia A & B participants without inhibitors	6/0	300 mg	Single dose	≥18 to <75	Completed	No

Study	Description	Population	N Treated (Active/ Placebo)	Dose(s) / Frequency	Duration	Age (Years)	Study Status	Included in Type II Variation
B7841014	Phase 1b	Severe haemophilia A without inhibitors on emicizumab therapy for ≥6 months	~10-15/0	150 mg SC injection QW[a] (DP: PFP)	Up to 120 days (17 weeks; up to 17 consecutive weekly doses)	≥12 to <75 years	Ongoing	No

a. Protocol-defined criteria allowed for dose escalation to 300 mg QW.
b. Protocol-defined criteria allowed for dose escalation to 150 mg QW.

2.3.2. Pharmacokinetics

Absorption

<u>New PK results of phase 3 Study B7841005 (only data from inhibitor patients)</u>

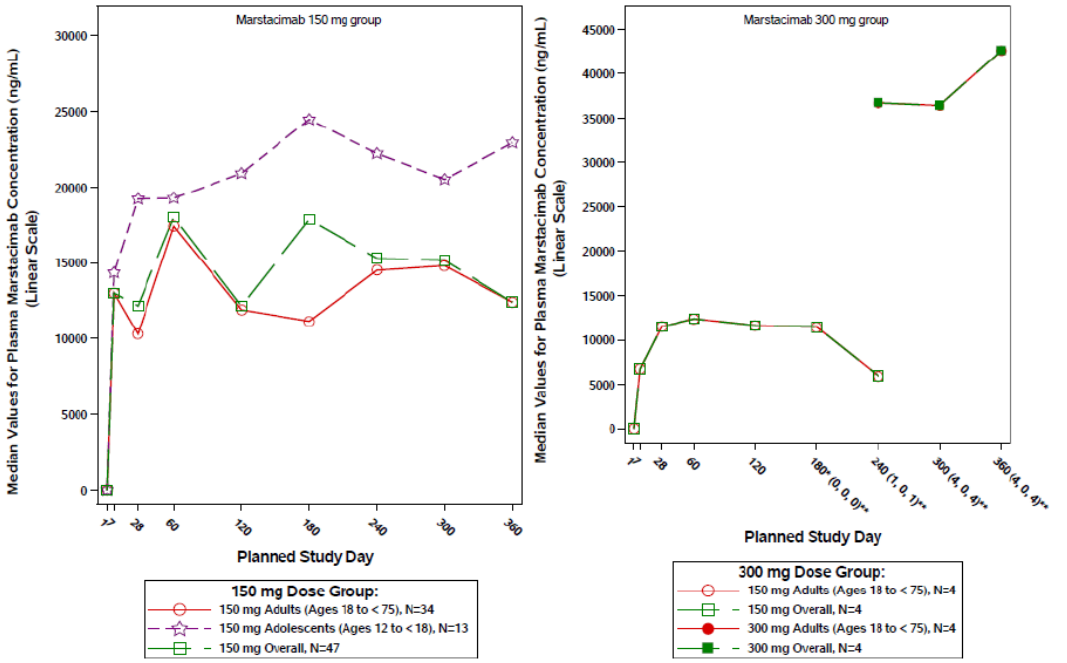
A total of 51 participants with haemophilia A and B (38 adults and 13 adolescents; 40 Hem A and 11 Hem B) from the inhibitor cohort receiving either 150 mg SC QW or 300 mg SC QW marstacimab had at least one evaluable PK concentration and contributed data for the PK analyses.

Following once weekly SC administration of 150 mg marstacimab (with an initial loading dose of 300 mg SC), plasma concentrations of marstacimab appeared to have reached steady state by approximately 60 days (i.e., by the 8th or 9th dose of weekly marstacimab dosing). Median steady-state marstacimab plasma concentrations in adults receiving 150 mg QW were approximately 11,000 - 17,000 ng/mL whereas median steady-state marstacimab plasma concentrations in adolescents were approximately 19,000 – 24,000 ng/mL.

In general, marstacimab concentrations were highly variable (%CV of approximately 58% - 81% in adults and 43% - 69% in adolescents for 150 mg SC QW), likely due to variability in actual post-dose sampling times and patient-specific properties.

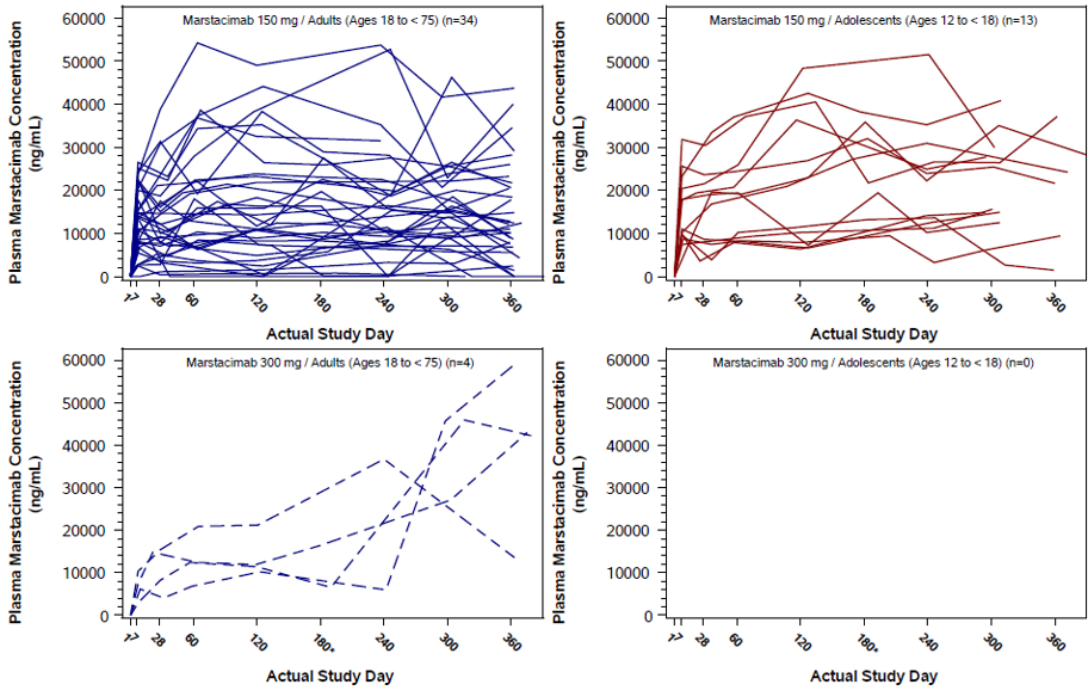
Marstacimab plasma concentrations increased following dose escalation to 300 mg SC QW and were higher than those seen with the 150 mg SC QW dose (Figure 1). As expected, greater than proportional increases in concentrations were seen with the higher dose, with median steady-state marstacimab concentrations for 300 mg SC QW ranging from 36,000 – 43,000 ng/mL (N=4 adults).

Figure 1. Median Marstacimab Plasma Concentration-Time Profiles (Linear Scale) Following Multiple Dose SC Administration of Marstacimab to Participants With Hemophilia A and B With Inhibitors (B7841005) by Dose Group and Age Group



N: Total number of participants in each dose and age group.
* Dose escalated to 300 mg on or after D180.
** Numbers (X, Y, Z) below the X-axis denote the number of dose escalated adult, adolescent and overall participants contributing data per analysis visit for 300 mg, respectively.
Unplanned readings were excluded from this presentation.
The lower limit of quantification was 100 ng/mL. Concentration values below the lower limit of quantification were set to zero.

Figure 14.4.4.6i Marstacimab Page 1 of 1
Plot of Individual Plasma Marstacimab Concentration - Time Plot by Dose Group and Age Group (Linear Scale) - Inhibitor Marstacimab Safety Set (Protocol B7841005_IN_CSR)



n: Total number of participants contributing to this plot in each dose and age group.
* Dose escalated to 300 mg on or after D180.
The lower limit of quantification was 100 ng/mL.
Concentration values below the lower limit of quantification were set to zero.

PK results of phase 3 Study B7841008 (only data from adolescent patients with or without inhibitors)

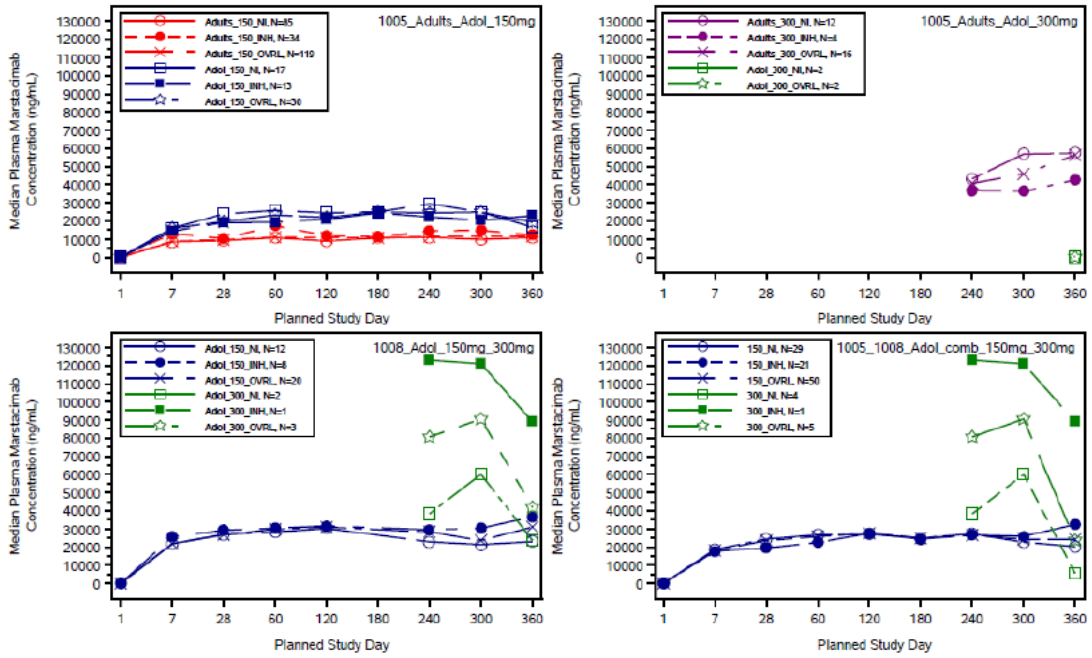
As of the cutoff date of 26 May 2025, a total of 23 adolescent participants with haemophilia A and B (9 inhibitor cohort participants and 14 non-inhibitor cohort participants) had at least 1 evaluable PK concentration and contributed data for the PK analyses.

Following once-weekly SC administration of 150 mg, plasma concentrations of marstacimab appeared to have reached steady state by approximately 60 days (i.e., by the 8th or 9th dose of weekly marstacimab dosing). Median steady-state marstacimab plasma concentrations in adolescents receiving 150 mg SC QW were approximately 30,000 - 37,000 ng/mL in participants with inhibitors, 21,000 - 30,000 in participants without inhibitors and 24,000 - 31,000 in the overall population.

In general, marstacimab concentrations are highly variable (%CV of approximately 62% -86% in participants with inhibitors and 51% - 131% in participants without inhibitors for 150 mg SC QW), likely due to variability in actual post-dose sampling times and patient-specific properties.

Marstacimab plasma concentrations increased following dose escalation to 300 mg SC QW and were higher than those observed with the 150 mg SC QW dose. As expected, greater than proportional increases in concentrations were observed for the higher dose of 300 mg SC QW, with concentrations (across time points) ranging from 89000 – 123000 ng/mL in 1 inhibitor cohort participant compared to mean values ranging from 24000 - 60000 ng/mL for 2 non-inhibitor cohort participants.

Figure 2: Plot of median values for plasma marstacimab concentration (ng/mL) versus time by phase 3 study and dose group (linear scale) – marstacimab safety set



Data for the non-escalated dose is reported from the non-escalated dose group only. For the escalated dose, only data after dose escalation is reported from the escalated dose group.
N: Total number of participants in the treatment group.
Unplanned readings have been excluded from this presentation.
Dose escalation was allowed on or after Day 180 in B7841005 and on or after Day 90 in B7841008.

Absorption analysis across all available studies

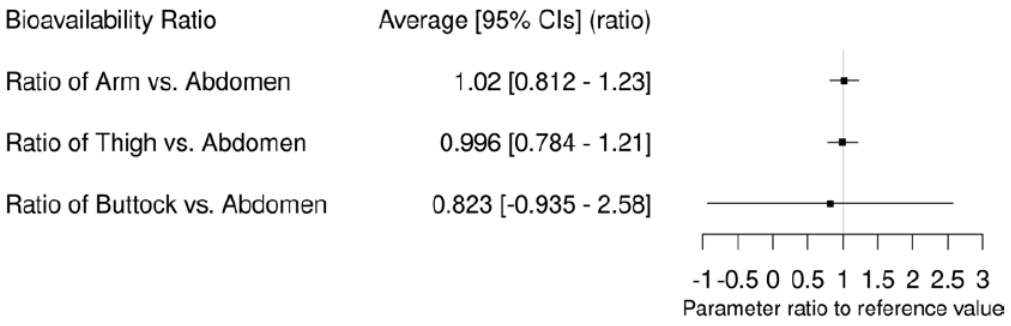
Following single dose SC administration of marstacimab to healthy participants and haemophilia patients, median Tmax ranged from 48 – 108 hours (range: 48 – 146 hours) and 70 – 73 hours (range: 23 – 167 hours), respectively. Following multiple dose SC administration of marstacimab to haemophilia patients, median Tmax ranged from 23 - 59 hours (range: 22 – 97 hours).

Bioavailability (BA) of SC dosing compared to the IV reference dose following single dose administration was 27%.

Population PK analysis estimated marstacimab BA following SC administration to be approximately 71% (6.5% RSE; 95% CI: 67% to 73%). The difference in the BA estimate between single dose administration (NCA analysis) and multiple dose administration (population PK) is likely attributed to the nonlinearity in marstacimab PK at higher concentrations. For drugs that exhibit nonlinear PK, estimation of BA using ratio of dose-normalized AUCs following IV and SC may lead to significant under- or over-estimation of BA.

Population analysis of the impact of site of administration (arm, thigh and abdomen) showed no statistically significant difference in marstacimab BA between arm, thigh and abdomen.

Figure 3: Forest plot of ratio of arm and thigh bioavailability as compared to abdomen



Item 59, repository artifact ID FI-64947837. CI - Confidence Interval; SE - Standard Error; The 95% CI was calculated using the SE in Table 21, i.e., 95% CI = Estimate ± 1.96 × SE (see Table 21 for the estimates of the bioavailability ratios and SE values.

No clinically meaningful differences are observed in population estimates for the combined inhibitor and non-inhibitor cohort population compared to those provided in the initial MAA for the non-inhibitor cohort population only.

Distribution

Following single dose IV administration in healthy participants marstacimab volume of distribution at steady-state (Vss) was 3.5 - 3.9 L. Following single dose SC administration in healthy participants and haemophilia patients, marstacimab Vz/F values ranged from 8.3 - 18.4 L.

Population PK analysis estimates (%RSE) for central volume of distribution (Vc), peripheral volume of distribution (Vp) and Vss were 3.7 (7.1%) L, 2.3 (10.4%) L and 6.0 L, respectively. This limited extravascular distribution suggests that marstacimab is restricted to the intravascular space.

There was a 55% difference in peripheral volume and a 30% difference in Vss compared to the values reported in initial MAA; these differences are not considered to be clinically meaningful.

Based on the updated population PK analysis, peripheral volume of distribution (V_p; now: 2.3 L, before: 5L) and consequently also volume of distribution at steady state (V_{ss}; update: 6 L, initial MA: 8.6 L) are lower compared to previous calculations presented in the EPAR for the initial MA. This corroborates the limited extravascular distribution of marstacimab.

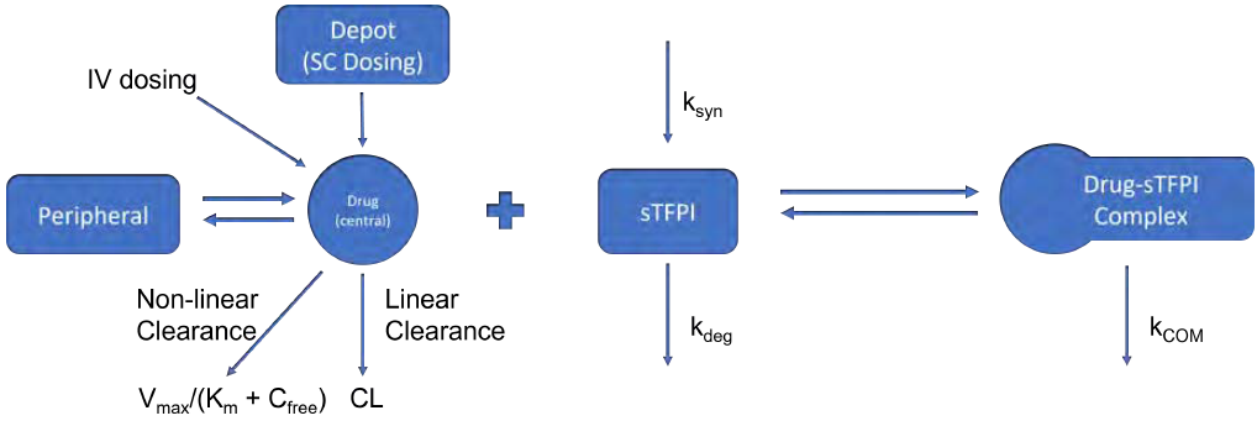
Elimination

Excretion studies were not conducted with marstacimab. Based on the molecular weight, marstacimab is expected to undergo catabolic degradation and is not expected to be renally cleared.

Marstacimab total CL/F following weekly SC administration to haemophilia patients ranged from 0.03 - 0.05 L/hr, based on NCA.

For the population PK analysis, marstacimab elimination was divided into linear and non-linear clearance (see Figure below).

Figure 4: Schematic of the final population PK model



Item 15, repository artifact ID FI-42662813.

The non-linear part was added to account for the drug binding to bound forms of TFPI. The estimated linear CL, Michaelis-Menten constant (Km) for the drug's non-linear clearance and maximum saturable elimination rate (Vmax) for the drug's nonlinear clearance (presented as population value (RSE%) in the final population PK analysis were 0.0169 (9.1%) L/hr, 3.88 (8.4%) nM and 0.65 (5.3%) nM/hr, respectively (see table 3 below).

Time of drug disappearance analysis using population PK model showed that 90% of marstacimab is expected to be eliminated within approximately 1 month after the last dose, with a median time of 7 – 11 days for 50% drug disappearance, i.e., elimination half-life. Time of drug disappearance metric is associated with pure elimination of the drug and reflects the time taken for the drug to be eliminated from the body.

Dose proportionality and time dependencies

Population PK analysis using a power model [AUCss = mDoseb or log AUCss = b*log(Dose) + m] as described by Wolfsegger et al was used to assess the dose proportionality of marstacimab in patients with haemophilia with and without inhibitors over a range of 3 doses (150 mg, 300 mg and 450 mg). Results showed point estimate value of m (intercept) to be 5.42 (95% CI: 0.96 – 9.88) and point estimate value of b (the proportionality exponent or slope in the linearized equation) to be 1.82 (95% CI: -3.43 – 7.07). Based on the point estimate of 1.82 for slope (p-value = 0.142), a $2^{1.82} = 3.53$-fold increase in AUCss is expected for a 2-fold increase in dose. Due to the high variability in the data, the 95% CI for b contained 1 and as such, deviation from linearity cannot be concluded even though greater than proportional increases are seen in AUCss in the 150 mg to 450 mg dose range (Initial MAA).

Population model-predicted estimates (median) for marstacimab AUCss in adults were 2220 µg·hr/mL (2.5 – 97.5 percentile: 152 – 8340 µg·hr/mL) and 9130 µg·hr/mL (2.5 – 97.5 percentile: 3250 – 20400 µg·hr/mL) for 150 mg SC QW and 300 mg SC QW respectively; approximately a 4.11-fold increase for a 2-fold increase in dose. Similar trends were also seen for model-predicted estimates of Cmax,ss.

In general, marstacimab exposures (AUCss and Cmax,ss) were seen to increase with slightly greater than proportional increases over the 150 mg to 450 mg SC dose range for participants with and without inhibitors.

No clinically meaningful differences are observed in the dose proportionality population estimates for the combined inhibitor and non-inhibitor cohort population compared to those provided in the initial MAA for non-inhibitor cohort population only.

Special populations

Population PK and PK/PD analyses using data from all healthy participant studies (B7841001, B7841009 and B7841010) as well as from adult and/or adolescent participants with haemophilia with and without inhibitors from completed studies (B7841002, B7841003, B7841005) and from the ongoing paediatric Phase 3 study (B7841008) were conducted to evaluate the effect of relevant intrinsic and extrinsic factors, i.e., demographics, race, creatinine clearance, hepatic impairment, anti-drug antibody (ADA) status, and inhibitor status on marstacimab PK and to support dosing regimens in various populations (e.g., haemophilia type, inhibitor vs. non-inhibitor) of different ages and weights (adolescents vs adults). A two-compartment model with TMDD and first order absorption was used to estimate PK parameters.

Table 3: Parameter estimates of the final population PK model

Parameter	Population Estimate	SE	RSE/CV (%)	Bootstrap Estimate	Bootstrap 95% CI
Central Volume, V_c (L)	3.73	0.265	7.11	3.5	3.16-3.8
Linear Clearance, CL (L/hr)	0.0169	0.00153	9.05	0.0166	0.0143-0.0195
Inter-compartmental Flow, Q (L/hr)	0.012	0.00148	12.4	0.0141	0.0131-0.017
Peripheral Volume, V_p (L)	2.26	0.234	10.4	2.49	2.3-2.89
Km for non-linear drug clearance, K_m, (nM)	3.88	0.327	8.44	3.22	2.56-3.46
Vmax for non-linear drug clearance, V_{max} (nM/hr)	0.652	0.0342	5.25	0.676	0.627-0.758
Bioavailability Fraction, F	0.711	0.046	6.47	0.697	0.67-0.725
Transfer rate from SC to Central compartment, K_a (1/hr)	0.00822	0.000562	6.83	0.00804	0.00727-0.00906
Baseline Total TFPI (nM)	3.74	0.0468	1.25	3.73	3.63-3.83
Degradation rate of free soluble TFPI, k_{deg} (1/hr)	0.0163	0.000825	5.06	0.0166	0.0152-0.0182
Degradation rate of drug-TFPI complex, k_{com} (1/hr)	0.000855	0.000108	12.7	0.000955	0.000899-0.00103
Quasi-steady state constant, KSS	71.3	2.75	3.85	69.6	64.2-75.1
Lag-time (hr)	2.41	0.05	2.07	2.45	2.18-2.74
Additive residual error on TFPI (log scale)	0.163	0.00193	1.19	0.162	0.152-0.173
Additive residual error on drug (log scale)	0.365	0.00296	0.812	0.366	0.333-0.402
Weight exponent on Central Volume	1.48	0.174	11.8	1.46	1.16-1.77
Weight exponent on Linear Clearance	1	0.198	19.7	0.98	0.604-1.34
Additional effect on CL for Healthy Population	0.0897	0.172	191	0.0448	-0.095-0.242
Additional effect on CL for Asian subjects	0.233	0.0913	39.1	0.226	0.0691-0.401
Additional effect on CL for ADA positive subjects	0.127	0.121	95.4	0.183	0.0121-0.363
Additional effect on CL for Mild-renal impairment	-0.135	0.0858	63.7	-0.14	-0.295-0.0132
Additional effect on CL for Hemophilia B subjects	-0.0109	0.0814	748	0.0113	-0.157-0.18
Additional effect on CL for Inhibitor subjects	0.137	0.112	81.8	0.122	-0.104-0.421
Additional effect on V_c for Inhibitor subjects	-0.0571	0.0761	133	-0.1	-0.3-0.0721
IIV on Central Volume, ($\omega^2_{V_c}$)	0.0975	0.0285	31.2	0.072	0.0417-0.109
Correlation coefficient between IIVs for CL and V_c	-0.83	0.129	36	-0.107	-0.165–0.0631
IIV on Linear Clearance (ω^2_{CL})	0.243	0.0448	49.3	0.211	0.13-0.323
IIV on Inter-compartmental Flow (ω^2_{Q}) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on Peripheral Volume ($\omega^2_{V_p}$) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on K_m ($\omega^2_{K_m}$) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on V_{max} ($\omega^2_{V_{max}}$)	0.0442	0.013	21	0.0311	0.0161-0.0524
IIV on Bioavailability fraction (ω^2_{F})	0.0794	0.112	28.2	0.119	0.0634-0.186
IIV on K_a ($\omega^2_{K_a}$)	0.296	0.0486	54.4	0.262	0.175-0.362
IIV on Baseline TFPI (ω^2_{BTFPI})	0.0233	0.00266	15.3	0.0229	0.0173-0.0293
IIV on K_{deg} ($\omega^2_{K_{deg}}$)	0.0153	0.0127	12.4	0.0294	0.00808-0.0657
IIV on K_{com} ($\omega^2_{K_{com}}$ (fixed))	0.0225	0	15	0.0225	0.0225-0.0225
IIV on KSS constant (ω^2_{KSS})	0.0752	0.0185	27.4	0.0771	0.041-0.114
IIV on lag-time (ω^2_{ALAG}) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225

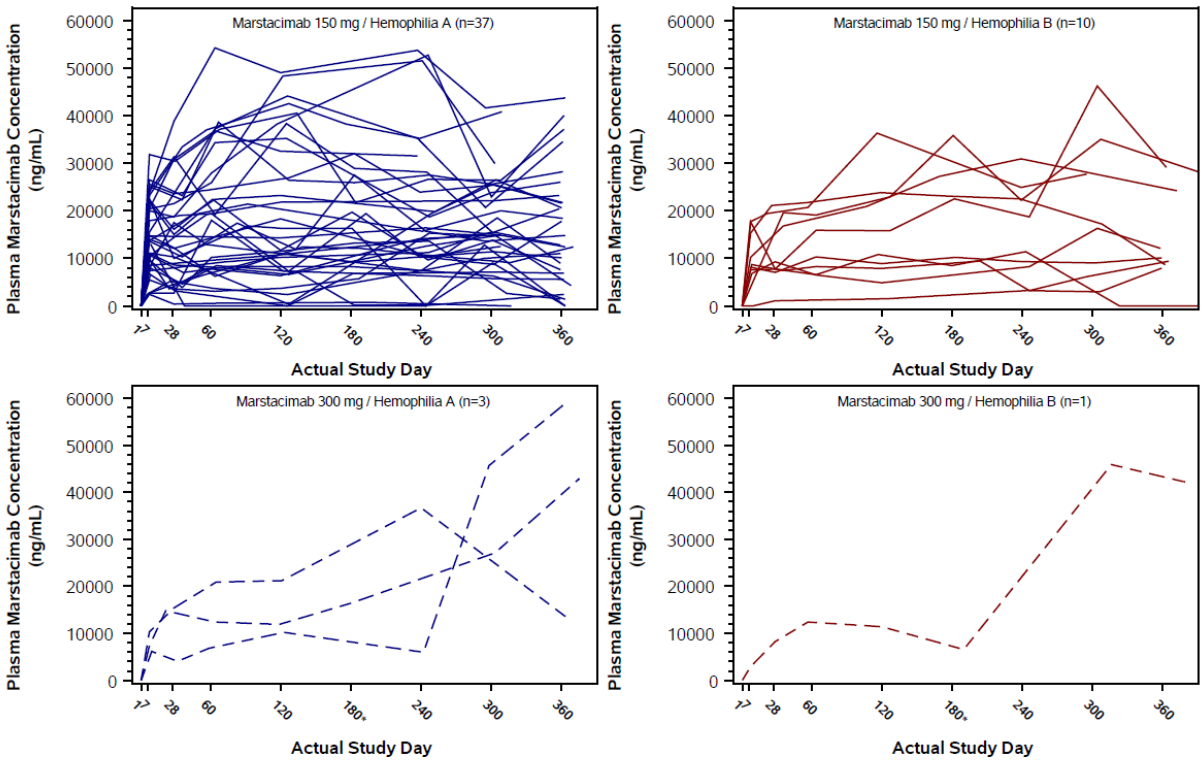
Item 34, repository artifact ID FI-64959935. Line 1 substituted. Bootstrap estimates were obtained from a bootstrap run with N = 500 samples using a PsN Bootstrap routine. SE - Standard Error; RSE - Relative Standard Error; CV - Coefficient of Variation; TFPI - Tissue Factor Pathway Inhibitor; KSS - Quasi-steady State Parameter; IIV - Inter-individual Variance. %RSE is provided for population (theta) parameters, %CV is provided for IIV parameters. Some of the IIVs were fixed to 15%CV. Residual variability was calculated on PK and TFPI via an additive error model on the log-scale with a thetarized (fixed) sigma parameter.

Haemophilia type

Population PK analysis did not show haemophilia type to be a clinically relevant covariate (1.1% lower CL in participants with haemophilia B compared to haemophilia A; 95% CI: -15.7% to 18%); there were no relevant differences in marstacimab PK between patients with haemophilia A and B.

Figure 5: Inhibitor safety set

Figure 14.4.4.5i Marstacimab
Plot of Individual Plasma Marstacimab Concentration - Time Plot by Dose Group and Hemophilia Type (Linear Scale) - Inhibitor Marstacimab Safety Set
(Protocol B7841005_IN_CSR)
Page 1 of 1



Weight

Weight was an important covariate to describe the pharmacokinetics of marstacimab in both participants with and without inhibitors. Normalized weight was included as a structural covariate on Vc, and CL, Q and Vp. The allometric constants for CL and Vc were estimated to be 1.0 and 1.48 respectively.

Marstacimab concentrations (geometric mean AUCss, Cmax,ss and Cmin,ss) were 2.6 to 3.2-fold higher in adolescents (baseline weight range: 25 – 94 kg) compared to adult (baseline weight range: 38 – 120 kg) patients with haemophilia. Differences in body weights between the 2 groups account for these exposure differences.

Table 4: Absolute and weight - normalised linear clearance and central volume

Variable	Type 1	Type 2
Age Type	Adolescents	Adults
Subjects	55	169
Geometric Mean CL (L/hr)	0.0139	0.0175
Range CL (L/hr)	0.00395 - 0.0341	0.00605 - 0.0749
Difference in Geometric Mean CL from Adults (%)	-20.6	.
Geometric Mean Weight adjusted CL (CL/W) (L/hr/kg)	0.000269	0.000255
Range CL/W (L/hr/kg)	8.82e-05 - 0.000611	8.65e-05 - 0.000902
Difference in Geometric Mean CL/W from Adults (%)	5.49	.
Geometric Mean Vc (L)	2.4	3.75
Range Vc (L)	0.863 - 7.11	1.03 - 9.31
Difference in Geometric Mean Vc from Adults (%)	-36	.
Geometric Mean weight adjusted Vc (Vc/W) (L/kg)	0.0465	0.0547
Range Vc/W (L/kg)	0.028 - 0.0945	0.0263 - 0.0945
Difference in Geometric Mean Vc/W from Adults (%)	-15	.
Patient Type	Healthy	Hemophilia
Subjects	63	224
Geometric Mean Weight adjusted CL (CL/W) (L/hr/kg)	0.000267	0.000259
Range CL/W (L/hr/kg)	0.000119 - 0.000799	8.65e-05 - 0.000902
Difference in Geometric Mean CL/W from Hemophilia Subjects (%)	3.09	.
Race Type	Asian	Non-Asian
Subjects	105	119
Geometric Mean Weight adjusted CL (CL/W) (L/hr/kg)	0.000292	0.000232
Range CL/W (L/hr/kg)	0.000118 - 0.000902	8.65e-05 - 0.000528
Difference in Geometric Mean CL/W from Non-Asians (%)	25.9	.
Hepatic Impairment Type	Mild Impairment	None
Subjects	20	204
Geometric Mean Weight adjusted CL (CL/W) (L/hr/kg)	0.000233	0.000261
Range CL/W (L/hr/kg)	8.65e-05 - 0.000807	8.82e-05 - 0.000902
Difference in Geometric Mean CL/W from No Hepatic Impairment Subjects (%)	-10.7	.

Item 45, repository artifact ID FI-65318717. Line 1 substituted. To better represent the central tendency of the expanded population and database, geometric mean is used to characterize the more robust population of participants contributing data to the analysis. CL - Linear Clearance (L/hr); Vc - Central Volume (L); CL/W - Weight normalized Linear Clearance (L/hr/kg); Vc/W - Weight normalized Central Volume (L/kg). For calculating hepatic impairment type, participants who had Bilirubin $\leq$ 40 umol/L and AST $\leq$ 20 umol/L were considered as having no hepatic impairment.

Inhibitor status (participants with inhibitors vs participants without inhibitors)

Effect of presence of inhibitors (i.e. inhibitor status) on marstacimab PK was evaluated using population PK analysis with inhibitor status as a covariate and NCA analysis. Population PK analysis showed that marstacimab linear CL was 13.7% (RSE 81.8%) higher in participants with haemophilia with inhibitors compared to without inhibitors. Difference in Vc between the 2 population groups was 5.7% (RSE 133%). RSEs for these estimates were high and the 95% CI for both contained 0 and as such, these effects are not considered to be clinically relevant. Comparison of model PK parameters shows good consistency between inhibitor cohort and non-inhibitor cohort participants. Although slight

differences are seen in secondary PK parameters (Cmax,ss, Cmin,ss AUCss, accumulation ratio etc) between the inhibitor cohort and non-inhibitor cohort populations, given the high variability, the observed differences are not considered to be clinically meaningful. For the most part, an overlap is seen in the 2.5th – 97.5th percentiles of the parameter values (Table 6 further below).

Age

Effect of age was not included as a covariate in the model since the haemophilia population in the clinical studies was a young population with median age of 27 years (range: 12 – 74 years, number of participants with haemophilia >65 years = 2) and expected differences in marstacimab PK between adolescents and adults were mostly accounted by including weight as a covariate in the model.

Race

Comparison of NCA PK parameters from Asian population (Japanese and Chinese) to non-Asian populations in Phase 1 studies did not show clinically relevant differences and observed differences were explained by weight differences.

Population PK analysis showed that the difference in CL values between Asians and Non-Asians participants with and without inhibitors was 23.3% (RSE of 39.1%). Difference in median individual weight-adjusted CL between Asian and non-Asian participants was approximately 26%.

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 or AST > ULN). Mild hepatic impairment did not have a clinically relevant impact in marstacimab CL. Population analysis of the effect of hepatic impairment on marstacimab CL showed a 10.7% lower CL with mild hepatic impairment. No dose adjustment is required for mild hepatic impairment. There are no data available on the use of marstacimab in patients with moderate or severe hepatic impairment.

Renal Impairment

Clinical studies have not been conducted to evaluate the effect of renal impairment as renal clearance is not considered important for elimination of mAbs due to their large size and inefficient filtration through the glomerulus.

All patients with haemophilia A and B in the population pharmacokinetic analysis had normal renal function (N = 198; eGFR ≥90 mL/min/1.73 m2) or mild renal impairment (N = 25; eGFR of 60 89 mL/min/1.73 m2).

Mild renal impairment did not have a clinically relevant impact in marstacimab CL. Population analysis of the effect of renal impairment on marstacimab CL showed a 13.5% lower CL with mild renal impairment (95% CI: -29.5% to 1.3%). There are no data available on the use of marstacimab in patients with moderate or severe renal impairment.

Steady-state drug exposures and accumulation (participants with and without inhibitors)

Following weekly SC administration of marstacimab to patients with haemophilia with and without inhibitors, marstacimab concentrations approached steady state by Day 7 (following a loading dose of 300 mg SC marstacimab) and were at steady state by approximately 60 days (i.e., by the 8th or 9th dose of weekly SC marstacimab, within ~ 3 effective half-lives).

Based on population PK analysis, marstacimab effective t½ (geometric mean), calculated from the accumulation ratios, ranged from approximately 18 – 22 days across both adults and adolescents and across dose groups. Effective half-life of a drug is based on drug accumulation ratio (which is dependent on absorption, and linear and non-linear clearances) and dosing interval and plays a role in time taken to reach steady-state and drug elimination. This metric is not reflective of pure elimination of the drug.

Table 5: Summary of secondary PK parameters by dosing regimen

Parameter	150 mg (Adults)	300 mg (Adults)	150 mg (Adolescents)	300 mg (Adolescents)
Subjects (N)	133	36	50	5
Mean $C_{min,ss}$ (ng/mL) (% CV)	14000 (90.4)	53000 (52.7)	32400 (71.8)	63300 (66.3)
Geometric Mean $C_{min,ss}$ (ng/mL)	7940	46400	25600	51400
Median $C_{min,ss}$ (ng/mL) (2.5 - 97.5%ile)	11000 (388 - 44800)	47900 (15300 - 103000)	28400 (4720 - 105000)	49300 (20900 - 110000)
Mean $C_{max,ss}$ (ng/mL) (% CV)	18800 (76.4)	64400 (50)	40400 (64.9)	79300 (52.4)
Geometric Mean $C_{max,ss}$ (ng/mL)	13200	57100	33800	69000
Median $C_{max,ss}$ (ng/mL) (2.5 - 97.5%ile)	14800 (1290 - 52200)	58400 (21400 - 131000)	34100 (8800 - 124000)	70300 (29500 - 122000)
Mean $C_{avg,ss}$ (ng/mL) (% CV)	17100 (80.4)	60400 (50.7)	37600 (67)	73500 (56.8)
Geometric Mean $C_{avg,ss}$ (ng/mL)	11400	53500	31000	62900
Median $C_{avg,ss}$ (ng/mL) (2.5 - 97.5%ile)	13200 (904 - 49600)	54300 (19300 - 121000)	32300 (7360 - 118000)	54600 (27200 - 119000)
Mean AUC_{ss} (ng·h/mL) (% CV)	2870000 (80.4)	10200000 (50.7)	6310000 (67)	12300000 (56.8)
Geometric Mean AUC_{ss} (ng·h/mL)	1920000	8980000	5210000	10600000
Median AUC_{ss} (ng·h/mL) (2.5 - 97.5%ile)	2220000 (152000 - 8340000)	9130000 (3250000 - 20400000)	5430000 (1240000 - 19800000)	9180000 (4580000 - 19900000)
Mean ACCR (% CV)	5.18 (62.8)	5.96 (64.7)	5.13 (64.9)	5.04 (47)
Geometric Mean ACCR	4.38	5.14	4.48	4.45
Median ACCR (2.5 - 97.5%ile)	4.63 (1.49 - 12.9)	4.81 (2.49 - 16.4)	4.53 (1.89 - 11.4)	4.64 (1.91 - 7.81)
Mean effective $t_{1/2}$ (days) (% CV)	22.6 (70.3)	26.4 (71)	22.3 (72.5)	21.9 (53.1)
Geometric Mean effective $t_{1/2}$ (days)	18.0	22.0	18.8	18.3
Median effective $t_{1/2}$ (days) (2.5 - 97.5%ile)	19.9 (4.37 - 60)	20.8 (9.44 - 77)	19.4 (6.46 - 52.7)	20 (6.47 - 35.4)

Item 54, repository artifact ID FI-65092914. Line 1 substituted. N- number of participants in the sub-group; SS - Steady State; ACCR - Accumulation Ratio

Based on population PK analysis, steady state accumulation ratio (geometric mean) ranged from approximately 4.4 – 5.1 across age groups and dose groups.

Table 6 below shows model estimated steady state Cmax,ss, Cmin,ss, Cavg,ss, AUCss, accumulation ratio and effective t½ for marstacimab for participants with and without inhibitors.

No clinically meaningful differences are observed in the population estimates for the combined inhibitor and non-inhibitor cohort population compared to those provided in the initial MAA for non-inhibitor cohort population only.

Table 6: Summary of marstacimab secondary PK parameters by age group and inhibitor status for 150 mg dosing regimen

Parameter	Adults Without Inhibitors	Adults With Inhibitors	Adolescents Without Inhibitors	Adolescents With Inhibitors
Participants (N)	99	34	29	21
Mean $C_{min,ss}$ (% CV)	13200 (95.5)	16100 (77.9)	30100 (74.5)	35500 (69)
Geometric Mean $C_{min,ss}$	7390	9790	23900	28300
Median $C_{min,ss}$ (2.5 - 97.5%ile)	9180 (395 - 45700)	13800 (367 - 43400)	26100 (4210 - 76500)	33100 (6810 - 90100)
Mean $C_{max,ss}$ (% CV)	17700 (79.6)	21900 (67.7)	37300 (65.9)	44700 (63.5)
Geometric Mean $C_{max,ss}$	12300	16100	31300	37500
Median $C_{max,ss}$ (2.5 - 97.5%ile)	13400 (1360 - 52700)	18500 (2560 - 51800)	32800 (8070 - 86300)	44400 (10800 - 108000)
Mean $C_{avg,ss}$ (% CV)	16100 (84.3)	19800 (70.3)	34800 (68.7)	41400 (65.2)
Geometric Mean $C_{avg,ss}$	10700	14000	28800	34300
Median $C_{avg,ss}$ (2.5 - 97.5%ile)	11800 (946 - 50200)	17000 (2280 - 47800)	30400 (6680 - 83300)	40000 (9480 - 101000)
Mean AUC_{ss} (% CV)	2710000 (84.3)	3320000 (70.3)	5850000 (68.7)	6960000 (65.2)
Geometric Mean AUC_{ss}	1790000	2350000	4840000	5770000
Median AUC_{ss} (2.5 - 97.5%ile)	1980000 (159000 - 8430000)	2850000 (382000 - 8040000)	5110000 (1120000 - 1.4+07)	6710000 (1590000 - 16900000)
Mean ACCR (% CV)	5.18 (58.3)	5.21 (75.3)	5.47 (71.8)	4.66 (48.7)
Geometric Mean ACCR	4.44	4.20	4.70	4.20
Median ACCR (2.5 - 97.5%ile)	4.63 (1.54 - 11.4)	4.37 (1.69 - 14.7)	4.7 (2.13 - 14.9)	4.08 (1.94 - 9.66)
Mean effective $t_{½}$ (% CV)	22.6 (65.2)	22.7 (84.2)	24 (79.6)	20.1 (55.2)
Geometric Mean effective $t_{½}$	18.3	17.0	19.9	17.4
Median effective $t_{½}$ (2.5 - 97.5%ile)	19.9 (4.59 - 52.7)	18.7 (5.36 - 69.1)	20.3 (7.64 - 69.7)	17.3 (6.67 - 44.4)

N: number of participants in the sub-group. 2.5 - 97.5%ile denotes 2.5th to 97.5th percentile.
Participants from the 150 mg SC QW (with a loading dose of 300 mg SC) and 450 mg SC QW (who transferred to 150 mg SC QW in study B7841003) dose groups from study B7841002 and participants from the 150 mg SC QW (with a loading dose of 300 mg SC) dose group in study B7841005 who did not escalate to 300 mg SC QW were categorized into the 150 mg SC QW dosing regimen.
Participants from the 300 mg SC QW dose groups in studies B7841002 and B7841003 along with participants from study B7841005 who got escalated to 300 mg SC QW were categorized into the 300 mg SC QW dosing regimen.
C_{min}, C_{max} and C_{avg} are in ng/mL, AUC is in ng•hr/mL and effective $t_{½}$ is in days.

2.3.3. Pharmacodynamics

Mechanism of action

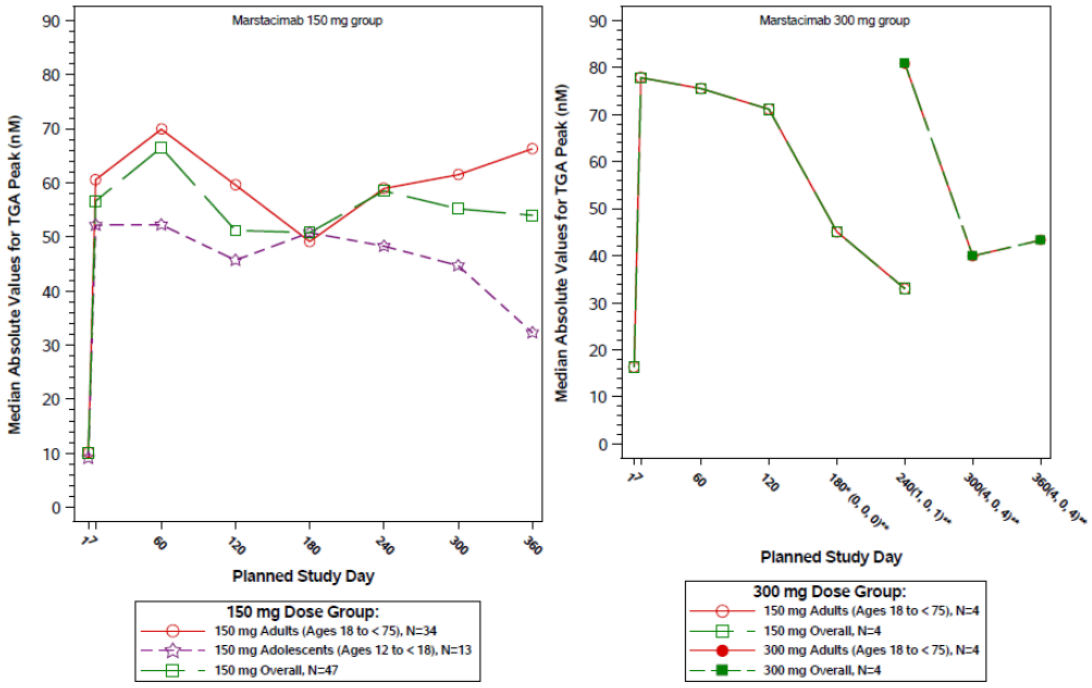
Marstacimab is a human monoclonal IgG1 antibody directed against the Kunitz domain 2 (K2) of tissue factor pathway inhibitor (TFPI), the primary inhibitor of the extrinsic coagulation cascade. TFPI initially binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2). The action of marstacimab to neutralise the inhibitory activity of TFPI may serve to enhance the extrinsic pathway and bypass deficiencies in the intrinsic pathway of coagulation by increasing free factor Xa available to increase thrombin generation and promote haemostasis.

Primary and secondary pharmacology

<u>New PD results of phase 3 Study B7841005 (only data from inhibitor patients)</u>

a) Peak Thrombin (TGA Peak):

Figure 6: Plot of median absolute values vs time for peak TGA (nM) by dose group and age group (B7841005)



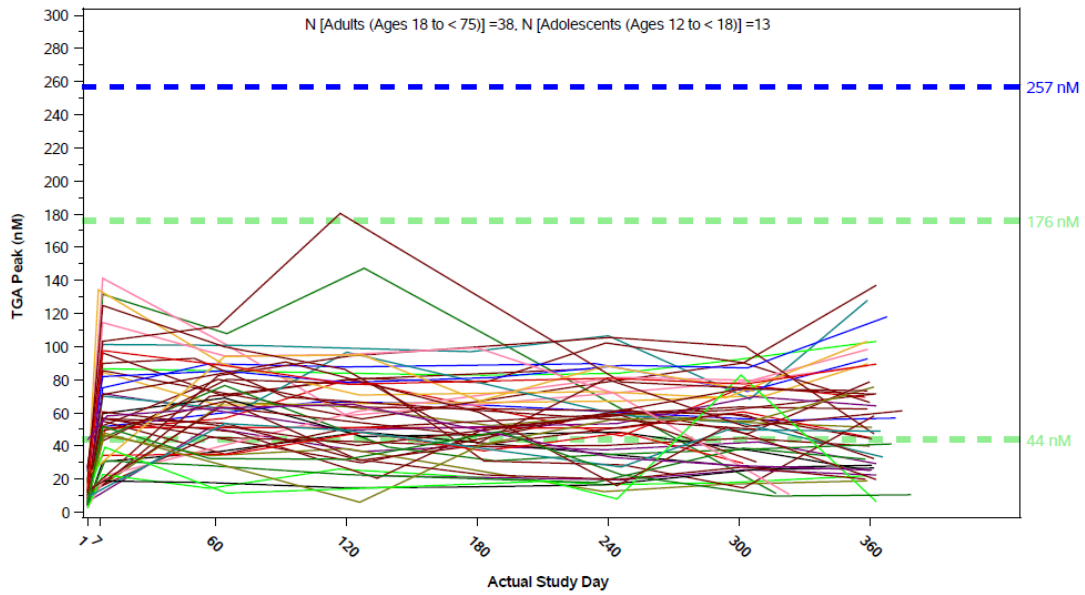
N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
* Dose escalated to 300 mg on or after D180.
** Numbers (X, Y, Z) below the X-axis denote the number of dose escalated adult, adolescent and overall participants contributing data per analysis visit for 300 mg, respectively.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:45) Source Data: adpd Table Generation: 30JUL2025 (08:33)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./ndal_cdisc/B7841005_IN_CSR/adptg_f001

Source: Module 5.3.5.2 B7841005 Final CSR Figure 14.5.1.2.1i

Post-treatment variability (geometric %CV) in peak TGA ranged from 26% - 81% across adults and adolescents (150 mg SC QW).

Figure 7: Inhibitor marstacimab safety set

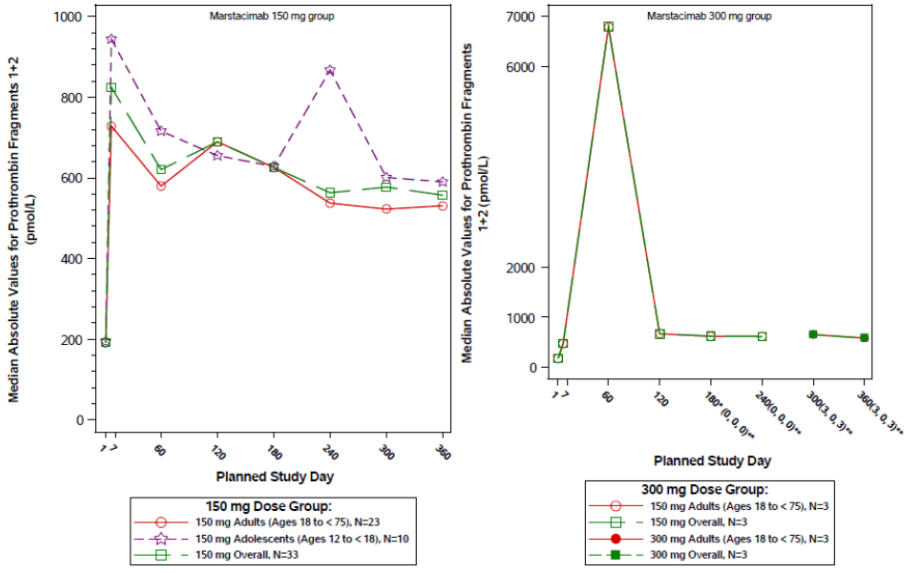
Figure 14.5.1.2.6i Marstacimab
Plot of Individual Absolute Values of TGA Peak (nM) for All Participants - Inhibitor Marstacimab Safety Set
(Protocol B7841005_IN_CSR)



N = total number of participants.
Dashed green line denotes 2.5th and 97.5th percentile of baseline predose values (normal physiological values) in healthy volunteers.
Dashed blue line denotes 97.5th percentile of values in healthy volunteers after single dose marstacimab administration.

b) PF 1+2:

Figure 8: Plot of median absolute value vs time for PF 1+2 (pmol/L) by dose group and age group (B7841005)



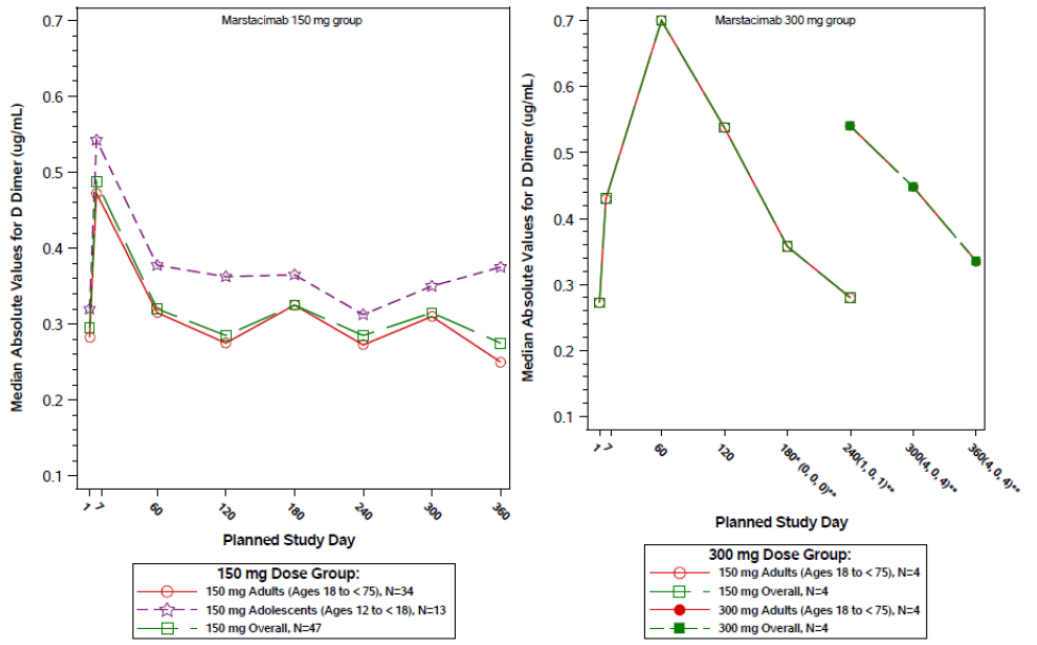
N: Total number of participants in each dose and age group with any non-MDx lab results.
Unplanned readings were excluded from this presentation.
Visit-level data excluded for 18 (out of a total of 19; 14 adults and 4 adolescents) China participants who had at least 1 result from MDx. Out of the 18 participants, data at all visits excluded for 15 participants and partial visit-level data excluded for 3 participants; total participants with at least 1 non-MDx PF 1+2 result = 36, 1 China participant did not have any PF1+2 data from MDx and is included in the summary statistics.
* Dose escalated to 300 mg on or after D180.
Note: Large difference in median values at D60 with and without MDx data is due to a high PF 1+2 value (greater than upper limit) seen in one non-MDx participant at that time point.
** Numbers (X, Y, Z) below the X-axis denote the number of dose escalated adult, adolescent and overall participants contributing data per analysis visit for 300 mg, respectively.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:45) Source Data: adpd Table Generation: 06AUG2025 (23:06)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./ndal_cdisc/B7841005_IN_CSR/adpf12_f001_s

Source: Module 5.3.5.2 B7841005 Final CSR Figure 14.5.2.2.1i

Post-treatment variability (geometric %CV) in PF 1+2 data ranged from 46% - 161% across adults and adolescents (150 mg SC QW).

c) D-dimer:

Figure 9: Plot of median absolute value vs time for D-dimer (µg/mL) by dose group and age group (B7841005)



N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
* Dose escalated to 300 mg on or after D180.
** Numbers (X, Y, Z) below the X-axis denote the number of dose escalated adult, adolescent and overall participants contributing data per analysis visit for 300 mg, respectively.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:45) Source Data: adpd Table Generation: 30JUL2025 (08:45)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./ndal_cdisc/B7841005_IN_CSR/adpdd_f001

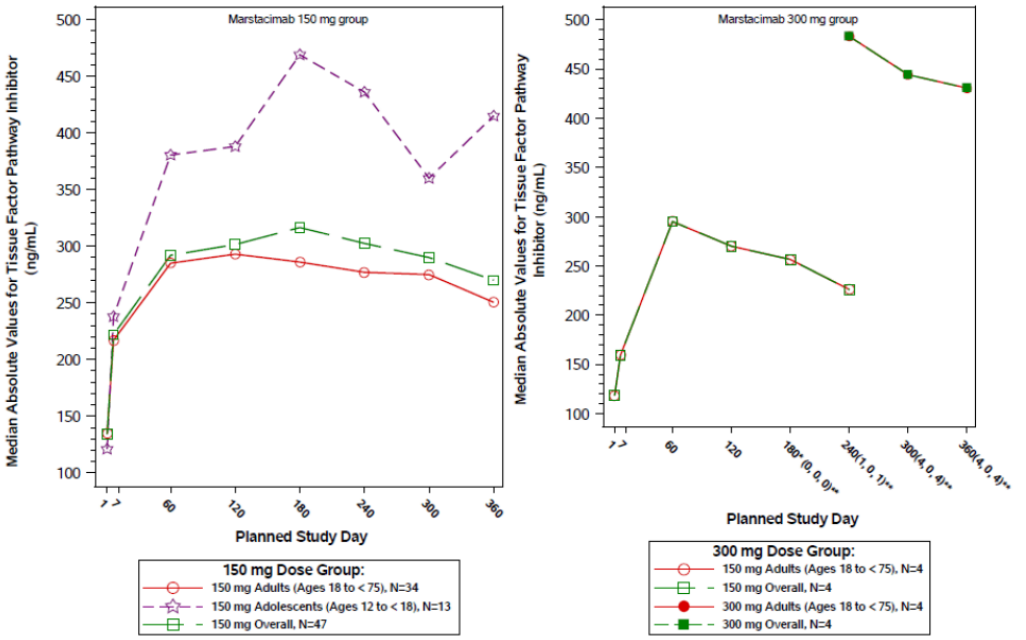
Source: Module 5.3.5.2 B7841005 Final CSR Figure 14.5.3.2.1i

Post-treatment variability (geometric %CV) in D dimer data ranged from 41% - 79% across adults and adolescents (150 mg SC QW).

d) Total TFPI

Following once-weekly SC administration of marstacimab, increases in total TFPI were observed in both adults and adolescents for both dose groups. This increase is consistent with binding of marstacimab to free TFPI resulting in delayed elimination of TFPI (bound to marstacimab) due to the much longer half-life of marstacimab as compared to target TFPI. Median total TFPI levels were seen to increase after the 1st dose, reach near-peak levels by Day 7 and peak levels by Day 60 and stay steady over time thereafter. Post-treatment variability (geometric %CV) in TFPI ranged from 5% - 50% across adults and adolescents (150 mg SC).

Figure 10: Plot of median value vs time for tissue factor pathway inhibitor (ng/mL) by dose group and age group (B7841005)

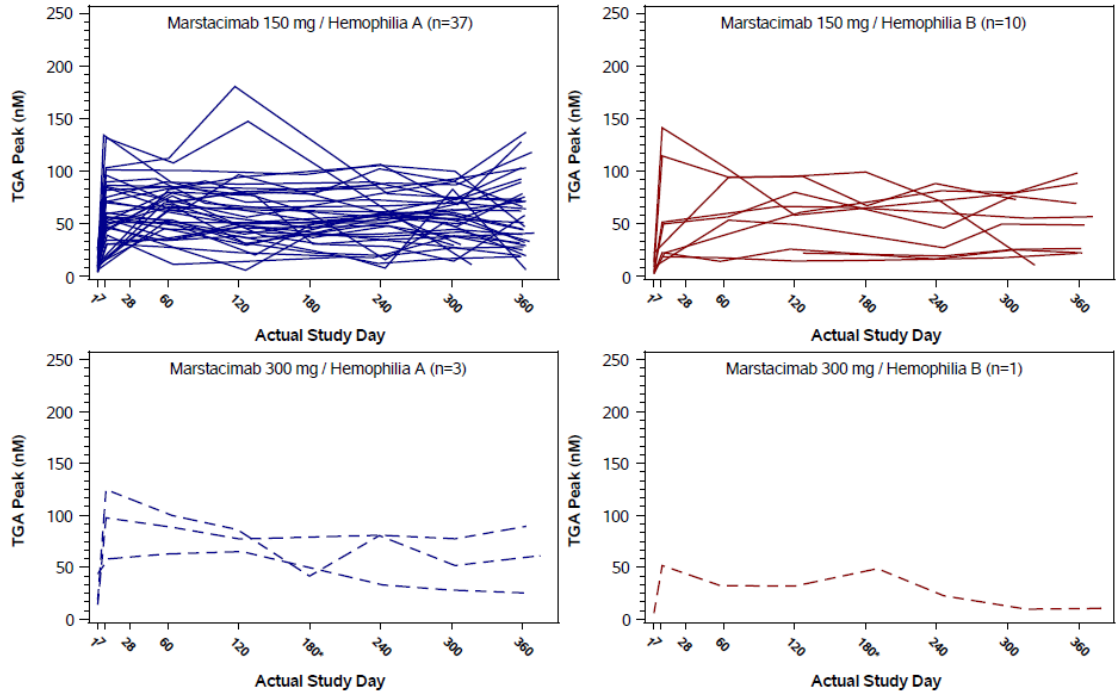


N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
* Dose escalated to 300 mg on or after D180.
** Numbers (X, Y, Z) below the X-axis denote the number of dose escalated adult, adolescent and overall participants contributing data per analysis visit for 300 mg, respectively.
PFIZER CONFIDENTIAL SUTM Creation: 03JUN2025 (16:45) Source Data: adpd Table Generation: 30JUL2025 (08:33)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./ndal_cdisc/B7841005_IN_CSR/adtfpi_f001

Overall, the new data from participants with inhibitors were comparable to known data from participants without inhibitors.

PD by haemophilia type

Figure 11: Plot of individual absolute value of TGA peak (nM) by dose group and haemophilia type



PD by inhibitor status (participants with inhibitors vs participants without inhibitors)

Higher baseline peak thrombin values were observed (for both age groups) in participants without inhibitors compared to participants with inhibitors. These observations are similar to the findings reported by Kavakli et al and Mancuso et al. In study B7841005, observed baseline peak thrombin values were highly variable, ranging from 3.6 – 141.6 nM in adult participants without inhibitors compared to 2.8 – 43.6 nM in adult participants with inhibitors. Across pooled studies B7841005 and B7841008, observed baseline peak thrombin values ranged from 5.3 – 128.2 nM in adolescent participants without inhibitors compared to 2.5 – 27.2 nM in adolescent participants with inhibitors. Comparison of model-based estimates showed ~ 50% lower baseline peak thrombin (PBASE) value in inhibitor cohort participants (median [range] = 9.2 [8.1 – 11.5] nM, compared to non-inhibitor cohort participants (median [range] = 17.8 [13.4 – 95.9] nM). No clinically relevant differences were observed in baseline values between participants with and without inhibitors for the other PD endpoints.

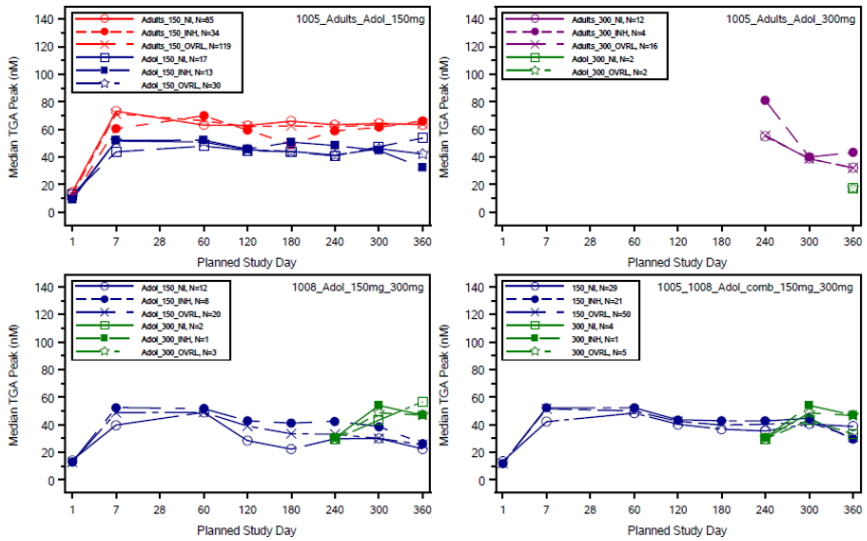
Following weekly SC marstacimab administration (150 mg SC QW), median peak thrombin values (across time points) ranged from 49 – 70 nM in adult participants with inhibitors (N=34) compared to 63 – 66 nM in adult participants without inhibitors (N=85). Median values ranged from 32 - 52 nM in adolescent participants with inhibitors (N=13) compared to 41 - 54 nM in adolescent participants without inhibitors (N=17) (Figure below, upper panel). Although post-dose median peak thrombin values are slightly lower in inhibitor cohort participants compared to non-inhibitor cohort participants (likely due to lower baseline values), these differences are not clinically meaningful. No clinically meaningful differences were observed in any of the other post-dose PD markers between participants with haemophilia with and without inhibitors.

PD results of phase 3 Study B7841008 (only data from adolescent patients with or without inhibitors)

The following plots compare data from the paediatric study B7841008 (lower panels) with the pivotal study B7841005 (upper panels).

a) Peak Thrombin (TGA Peak):

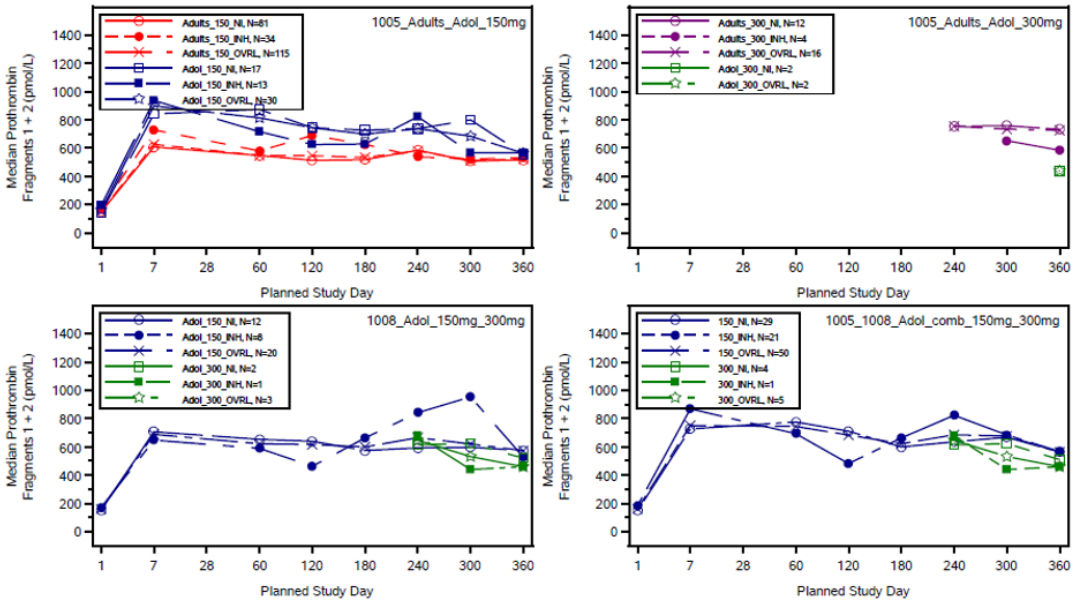
Figure 12: Plot of median absolute values for TGA peak (nmol) versus time by phase 3 study and dose group (nominal scale) - marstacimab dataset



Data for the non-escalated dose is reported from the non-escalated dose group only. For the escalated dose, only data after dose escalation is reported from the escalated dose group.
N: Total number of participants in the treatment group.
Unplanned readings have been excluded from this presentation.
Dose escalation was allowed on or after Day 180 in B7841005 and on or after Day 90 in B7841008

b) PF 1+2:

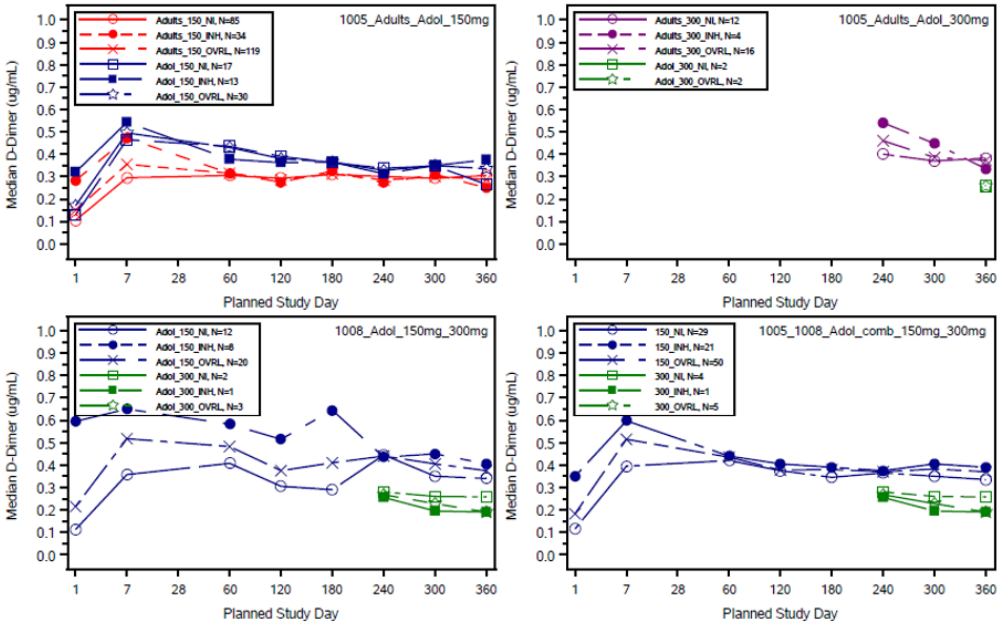
Figure 13: Plot of median absolute values for prothrombin fragments 1+2 (pmol/L) versus time by phase 3 study and dose group (nominal scale) – marstacimab dataset



Data for the non-escalated dose is reported from the non-escalated dose group only. For the escalated dose, only data after dose escalation is reported from the escalated dose group.
N: Total number of participants in the treatment group. Unplanned readings have been excluded from this presentation. Dose escalation was allowed on or after Day 180 in B7841005 and on or after Day 90 in B7841008.
For all studies, visit-level data are excluded for China participants who had at least 1 result from MDx.
PF 1+2 summary statistics for the B7841005 Non-Inhibitor participants are calculated after excluding visit-level PF1+2 results from MDx laboratory (to maintain consistency with the logic followed for B7841005 Inhibitor population in B7841005 Final CSR); as such, summary statistics are slightly different from summary statistics presented in the BLA SCP for B7841005 Non-Inhibitor population where PF 1+2 MDx data (applicable to 4 Non-Inhibitor China participants) were included in the summary statistics (reference to Errata Communication issued in 2024).

c) D-dimer:

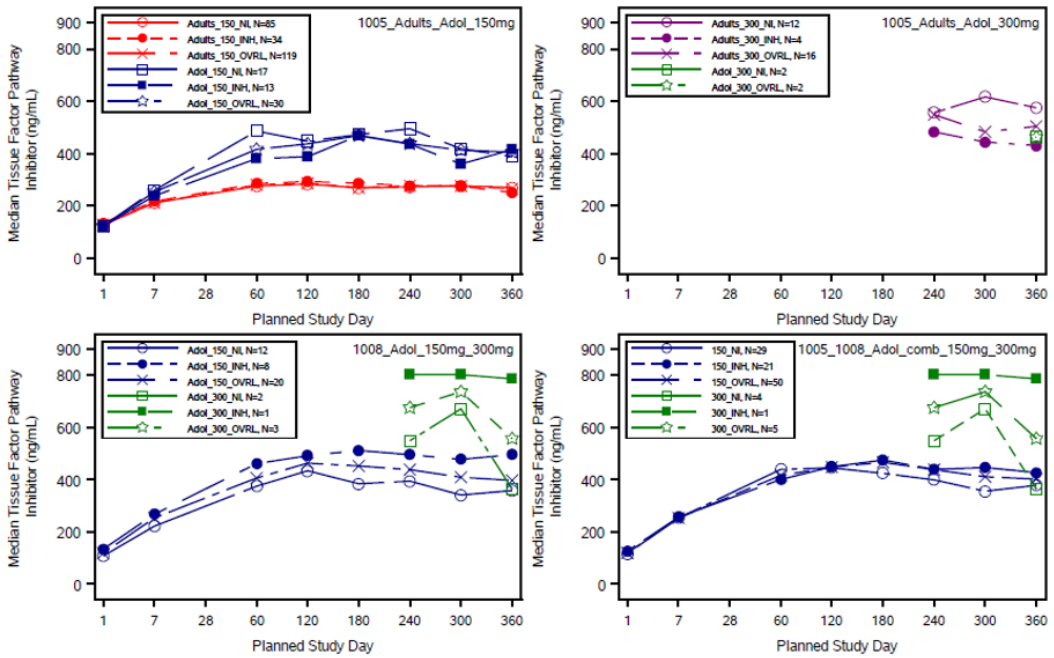
Figure 14: Plot of median absolute values for D-dimer (µg/mL) versus time by phase 3 study and soe group (nominal scale) – marstacimab dataset



Data for the non-escalated dose is reported from the non-escalated dose group only. For the escalated dose, only data after dose escalation is reported from the escalated dose group.
N: Total number of participants in the treatment group.
Unplanned readings have been excluded from this presentation.
Dose escalation was allowed on or after Day 180 in B7841005 and on or after Day 90 in B7841008.

d) Total TFPI:

Figure 15: Plot of median absolute values for tissue factor pathway inhibitor (µg/mL) versus time by phase 3 study and dose group (nominal scale) – marstacimab dataset



Data for the non-escalated dose is reported from the non-escalated dose group only. For the escalated dose, only data after dose escalation is reported from the escalated dose group.
N: Total number of participants in the treatment group.
Unplanned readings have been excluded from this presentation.
Dose escalation was allowed on or after Day 180 in B7841005 and on or after Day 90 in B7841008

2.3.4. Immunogenicity

None of the 51 evaluable participants had positive ADA titers at baseline. Of the 51 ADA-evaluable participants, 10 participants (19.6% incidence) were ADA positive (ADA+ve) (treatment-induced). Out of the 10 ADA+ve participants, 9 participants were adults (9 out of 38 adult participants; 23.7%) and 1 participant was an adolescent (1 out of 13 adolescent participants; 7.7%).

Table 7: Percent of participants with transient and persistent ADA and Nab response by age group – inhibitor marstacimab safety set (protocol B7841005_IN_CSR)

	Adults (Ages 18 to < 75) (N=38)		Adolescents (Ages 12 to < 18) (N=13)		Overall (N=51)	
Number (%) of Participants	ADA	NAb	ADA	NAb	ADA	NAb
ADA or NAb evaluable participants (N1)	38	9	13	1	51	10
Total treatment-emergent positive participants, N2/N1 (%)	9/ 38 (23.7)	2/ 9 (22.2)	1/ 13 (7.7)	0/ 1 (0.0)	10/ 51 (19.6)	2/ 10 (20.0)
Persistent, x1/N2 (%)	1/ 9 (11.1)	1/ 2 (50.0)	0/ 1 (0.0)	0/ 0	1/ 10 (10.0)	1/ 2 (50.0)
Transient, x2/N2 (%)	8/ 9 (88.9)	1/ 2 (50.0)	1/ 1 (100.0)	0/ 0	9/ 10 (90.0)	1/ 2 (50.0)
Indeterminate, x3/N2 (%)	0/ 9 (0.0)	0/ 2 (0.0)	0/ 1 (0.0)	0/ 0	0/ 10 (0.0)	0/ 2 (0.0)

ADA+: ADA positive; ADA-: ADA negative; NAb+: NAb positive; NAb-: NAb negative.
ADA evaluable: All participants with ≥1 post-treatment ADA result.
NAb evaluable: ADA+ participants only with ≥1 post-treatment NAb result; an ADA+ participant without any post-treatment NAb data is excluded from the analysis population.
ADA+ participant: A participant with ≥1 treatment-induced (Baseline ADA titer is missing or negative, and participant has ≥1 post-treatment positive ADA titer) or treatment-boosted (ie ≥4-fold dilution increase in ADA titer from baseline in ≥1 post-treatment sample) ADA response.
NAb+ participant: An ADA+ participant with ≥1 treatment-induced (Baseline NAb titer is missing or negative or ADA-, and participant has ≥1 post-treatment positive NAb titer) or treatment-boosted ≥4-fold dilution increase in NAb titer from baseline in ≥1 post-treatment sample) NAb response.
N=Number of participants who received at least one dose of marstacimab. N1 = Number of ADA or NAb evaluable participants; N2 = Number of ADA+ or NAb+ participants (treatment-induced or treatment-boosted);
x1 = number of ADA+ participants who show a persistent profile; x2 = number of ADA+ participants who show a transient profile; x3 = number of ADA+ participants who are not persistent or transient.
Percentages for evaluable are based on number of participants who received at least one dose of marstacimab.
Percentages for positive participants are based on number of evaluable participants.
Percentages for transient, persistent and indeterminate are based on number of ADA+ or NAb+ participants.
Refer to Table 16.2.8.5.16i (Immunogenicity Terms and Definitions) for definitions of Persistent, Transient and Indeterminate.

For the majority of the participants who developed ADAs, titers were low (maximum titer log10 value = 3.03, titer log10 cut off = 1.53) and seen by the 1st post-dose visit where assessed, i.e., Day 28 (total of 5/10 ADA+ve participants; 50.0%). ADAs were transient (in general, ADA positivity for <16 weeks at any time during the study) in 90.0% (9/10) and persistent (in general, ADA positivity for ≥16 weeks at any time during the study) in 10.0% (1/10) of the ADA+ve participants, indicative of a transient ADA profile in the majority of the participants (duration of ADA persistence in the 1 ADA-persistent participant was 297 days at end of study [titer log10 of 2.44]). ADAs were resolved in 9/10 (90.0%) participants by the end of the study.

Two (2) participants out of the 10 ADA+ve participants were NAb+ve (incidence relative to ADA+ve participants [2/10] = 20.0%; incidence relative to ADA-evaluable participants [2/51] = 3.9%). All NAbs were treatment-induced, with 1 NAb+ve participant with a persistent profile (duration of NAb positivity was ≥16 weeks; titer log10 range: 1.44 - 2.02, titer log10 cut off = 1.08) and 1 NAb+ve participant with a transient profile in nature (NAb positivity detected only at 1 sampling time; titer log10 = 1.08). No participants were NAb+ve at the end of the study.

Impact of anti-drug antibodies (ADAs) on PK data

Difference in geometric mean marstacimab concentrations between ADA+ve and ADA negative (ADA-ve) participants (based on geometric mean ratio for ADA+ve/ADA-ve) ranged from -36% to +19%. Although slightly lower geometric mean marstacimab concentrations (~10%-36% lower; Table 8) were reported in ADA+ve participants compared to ADA-ve participants, concentrations largely overlapped between these 2 groups, with concentrations in ADA+ve group contained within the concentration range observed in ADA-ve group.

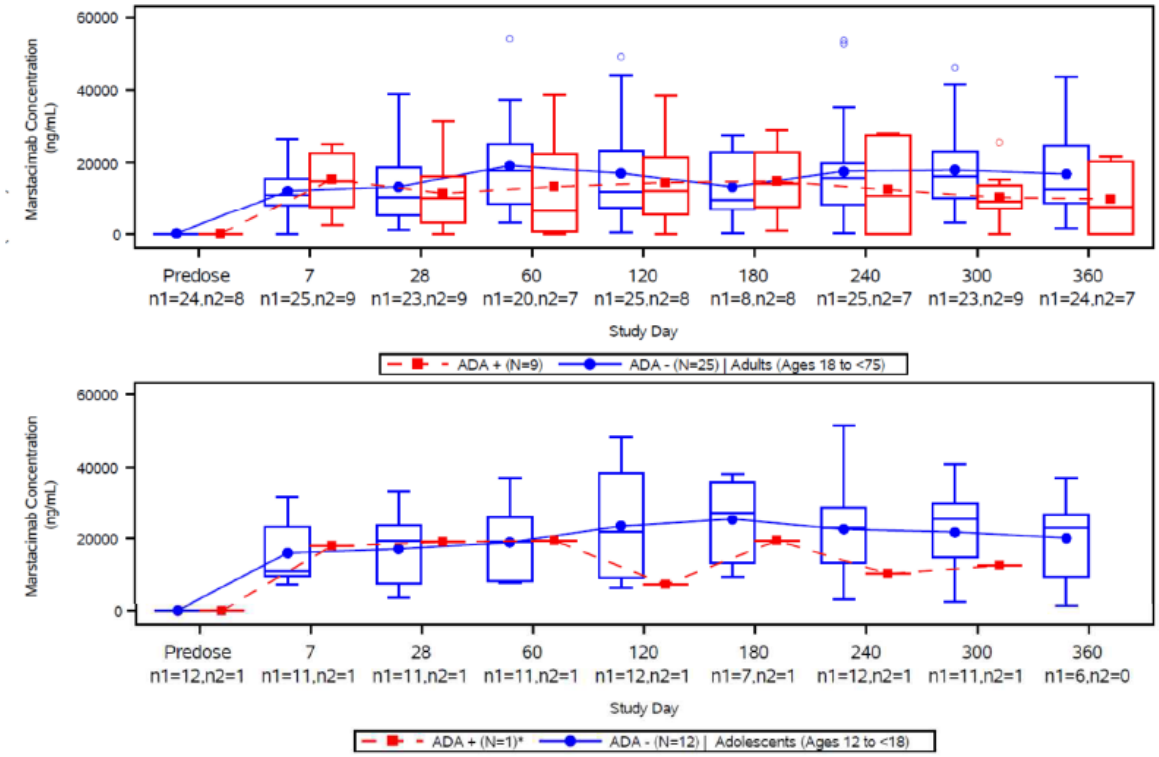
Table 8: Summary of marstacimab concentration geometric mean ratio and 90% CI for ADA +ve vs ADA -ve participants (both dose groups) – inhibitor marstacimab safety set

(Protocol B7841005_IN_CSR)

			Marstacimab geometric mean concentration (ng/mL)			
ARM	Analysis Visit	Total (N)	Overall ADA +ve	ADA +ve (n)	Overall ADA -ve	ADA -ve (n)
MARSTACIMAB	ATP D7	49	12894.2	10	10850.6	39
MARSTACIMAB	ATP D28	47	8579.3	9	10822.8	38
MARSTACIMAB	ATP D60	42	9599.7	7	14883.9	35
MARSTACIMAB	ATP D120	48	15206.2	7	13075.2	41
MARSTACIMAB	ATP D180	26	11084.0	9	12253.1	17
MARSTACIMAB	ATP D240	45	14520.8	6	14128.6	39
MARSTACIMAB	ATP D300	46	12252.3	8	17216.0	38
MARSTACIMAB	ATP D360	39	12340.1	5	14526.9	34

ARM	Analysis Visit	GMR (90% CI) ADA+/ADA-
MARSTACIMAB	ATP D7	1.19 (0.80, 1.77)
MARSTACIMAB	ATP D28	0.79 (0.45, 1.41)
MARSTACIMAB	ATP D60	0.64 (0.36, 1.16)
MARSTACIMAB	ATP D120	1.16 (0.60, 2.24)
MARSTACIMAB	ATP D180	0.90 (0.38, 2.16)
MARSTACIMAB	ATP D240	1.03 (0.50, 2.09)
MARSTACIMAB	ATP D300	0.71 (0.46, 1.10)
MARSTACIMAB	ATP D360	0.85 (0.41, 1.75)

Figure 16: Box plot of marstacimab plasma concentration (ng/mL) versus time by ADA status (marstacimab 150 mg) – marstacimab safety set



Impact of ADA and NAb on PD Data

Figure 17: Box plot of TGA peak (nM) versus time by ADA status (marstacimab 150 mg) – marstacimab safety set

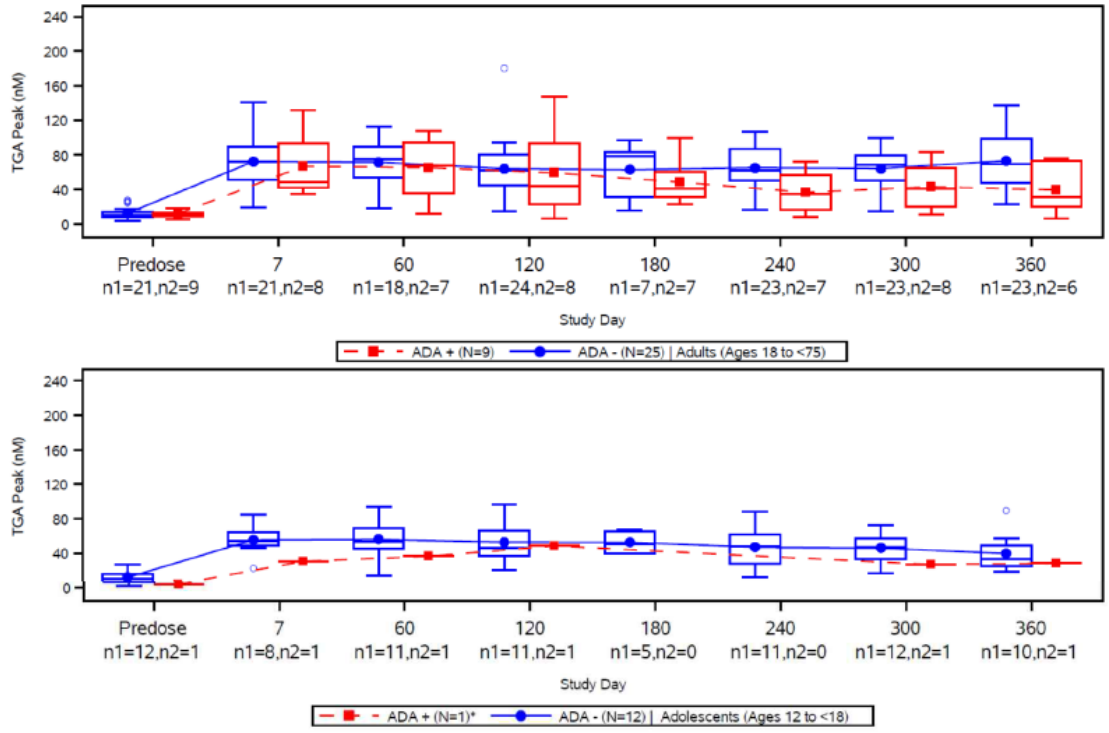


Figure 18: Box plot of prothrombin fragments 1+2vs. time (marstacimab) 150 mg SC QW dose group) – (excluding Mdx lab results) by ADA status – inhibitor marstacimab safety set

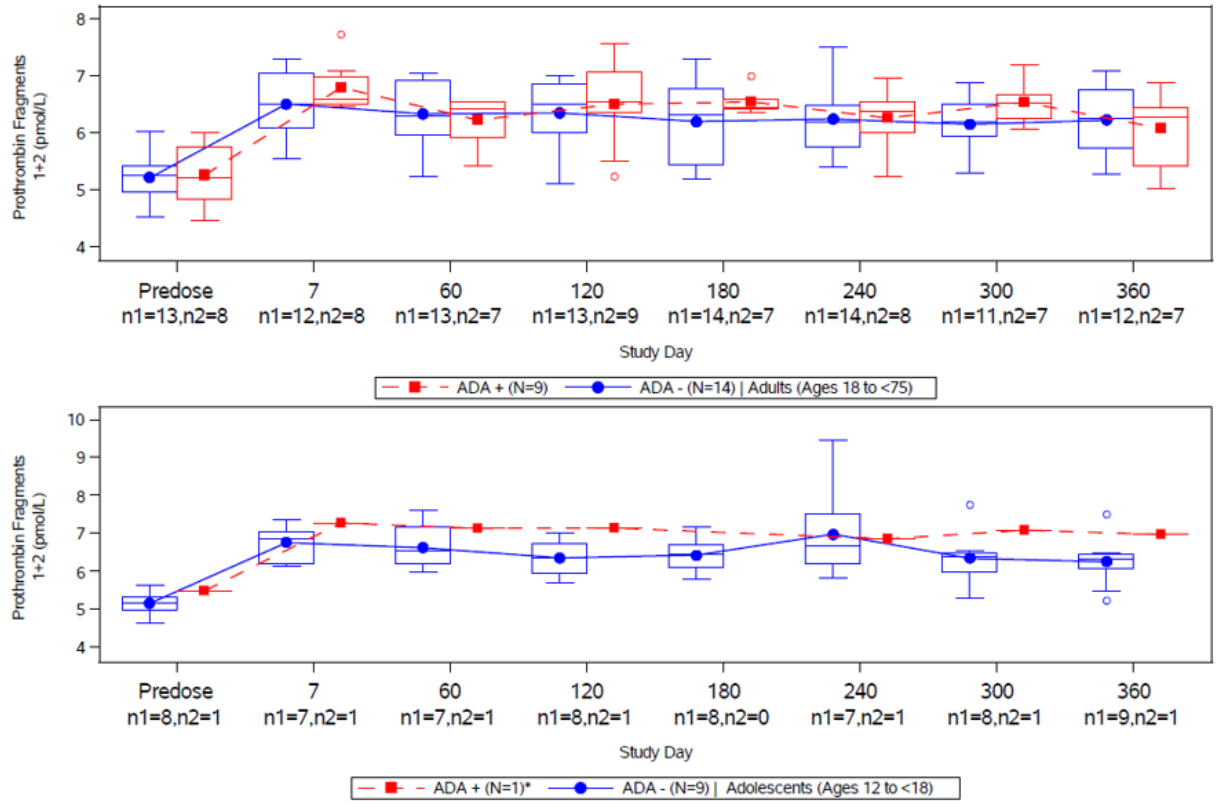


Figure 19: Box plot of D-dimer vs time (marstacimab 150 mg SC QW dose group) by ADA status – inhibitor marstacimab safety set

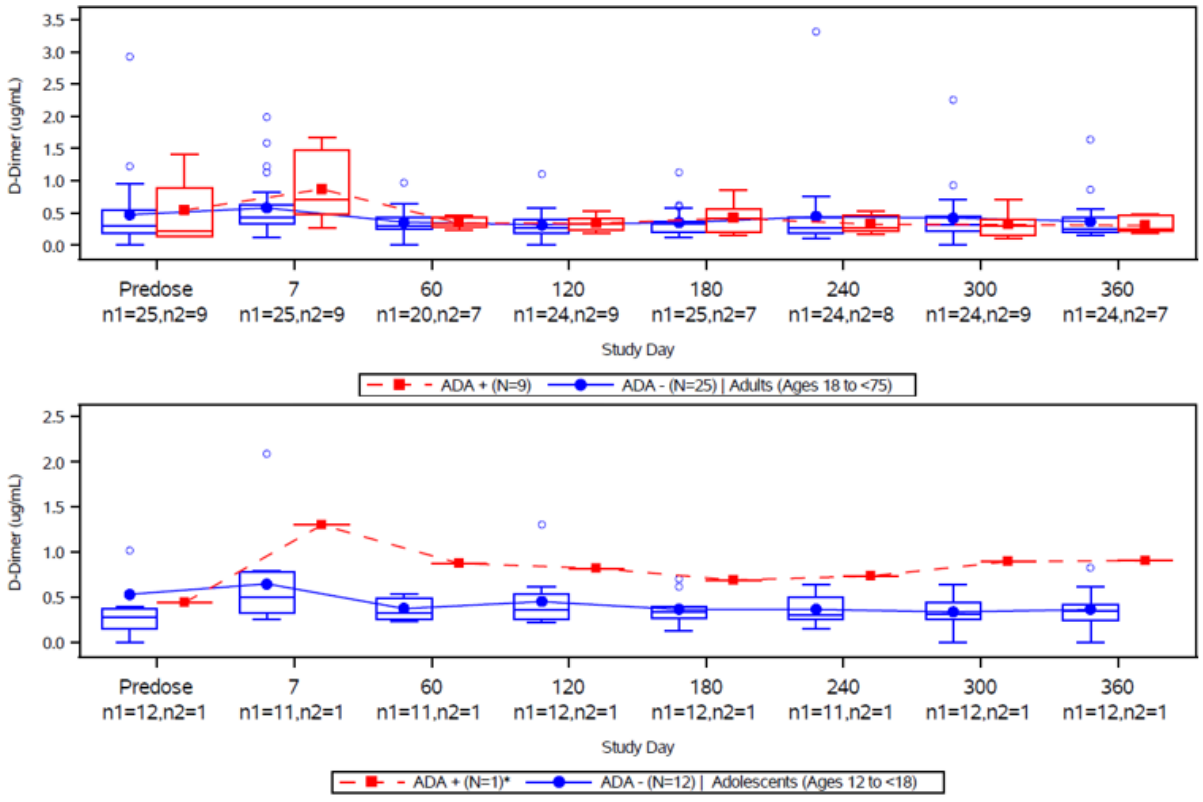
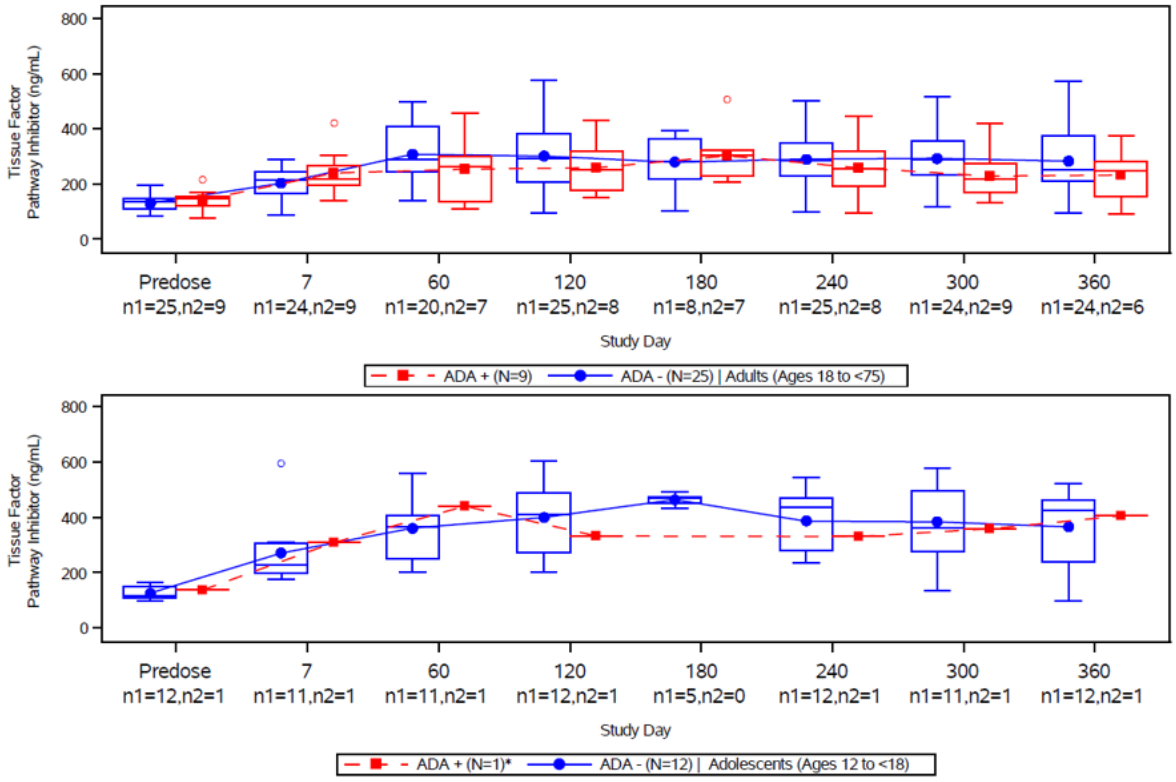


Figure 20: Box plot of tissue factor pathway inhibitor vs time (marstacimab 150 mg SC QW dose group) by ADA status – Inhibitor marstacimab safety set



Immunogenicity results for the paediatric study B7841008

As of the 26 May 2025 cut off, a total of 24 participants with haemophilia A and B with or without inhibitors (9 inhibitor cohort participants and 15 non-inhibitor cohort participants) ≥12 - <18 years of age provided at least 1 ADA result and were evaluable for ADA analysis. One (1) out of a total of 24 ADA-evaluable participants in the ≥12 - < 18 group had positive ADA titers at baseline. Of the 24 ADA-evaluable ≥12 - <18-year participants, 4 participants (16.7% incidence) were ADA+ve (all were treatment-induced). Out of the 4 ADA+ve participants, 3 (3 out of 9 inhibitor cohort participants; 33.3%) were inhibitor cohort participants and 1 (1 out of 15 non-inhibitor cohort participants; 6.7%) was a non-inhibitor cohort participant. ADA titers were low (maximum titer log10 value = 3.16, titer log10 cut off = 1.53). Out of the 4 ADA+ve participants, 2 (50.0%) were ADA+ve by the first assessed visit at Day 28. ADAs were transient (ADA positivity for <16 weeks at any time during the study) in 75.0% (3/4) and persistent (ADA positivity for ≥16 weeks at any time during the study) in 25.0% (1/4) of the ADA+ve participants, indicative of a transient ADA profile in the majority of the participants. Duration of ADA persistence in the 1 ADA-persistent participant was 300 days (titer log10 range: 2.27 – 3.16) and the participant was ADA+ve as of study cut-off (titer log10 of 2.27). ADAs were resolved in 3/4 (75.0%) participants by study cut-off.

One (1) participant (with inhibitor) out of the 4 ADA+ve participants was NAb+ve (incidence relative to ADA+ve participants [1/4] = 25.0%; incidence relative to ADA-evaluable participants [1/24] = 4.2%). NAbs were treatment-induced, low titer (maximum titer log10 value = 2.26, titer log10 cut off = 1.08) and persistent with a duration of NAb-persistence of 120 days (titer log10 range: 1.58 – 2.26, titer log10 cut off = 1.08). No participants were NAb+ve as of study cut-off.

Table 9: summary of marstacimab concentration geometric mean ratio and 90 % CI for ADA +ve vs. ADA -ve participants (≥12 to < 18 years, B7841008 interim analysis)

		Age ≥12 to								Age ≥12 to								Age ≥12 to							
		Marstacimab geometric mean concentration (ng/mL)								Marstacimab geometric mean concentration (ng/mL)								Marstacimab geometric mean concentration (ng/mL)							
ARM	Analysis Visit	Total (N1)	Overall ADA +ve	Geometric CV (%) ADA +ve	ADA +ve (n)	Overall ADA - ve	Geometric CV (%) ADA -ve	ADA -ve (n)	GMR (90% CI) ADA+/ADA-	Total (N1)	Overall ADA +ve	Geometric CV (%) ADA +ve	ADA +ve (n)	Overall ADA - ve	Geometric CV (%) ADA -ve	ADA -ve (n)	GMR (90% CI) ADA+/ADA-	Total (N1)	Overall ADA +ve	Geometric CV (%) ADA +ve	ADA +ve (n)	Overall ADA - ve	Geometric CV (%) ADA -ve	ADA -ve (n)	GMR (90% CI) ADA+/ADA-
MARSTACIMAB	DAY 7	22	27198.6	44	4	22006.5	70	18	1.24 (0.69, 2.20)	19	27198.6	44	4	22918.8	68	15	1.19 (0.67, 2.10)	3	-	-	0	17961.7	100	3	- (-, -)
MARSTACIMAB	DAY 28	23	27247.2	49	4	23063.1	86	19	1.18 (0.60, 2.31)	20	27247.2	49	4	25406.1	83	16	1.07 (0.55, 2.08)	3	-	-	0	13766.1	88	3	- (-, -)
MARSTACIMAB	DAY 60	23	18549.3	131	4	25723.7	101	19	0.72 (0.32, 1.63)	20	18549.3	131	4	29883.4	71	16	0.62 (0.31, 1.24)	3	-	-	0	11565.1	267	3	- (-, -)
MARSTACIMAB	DAY 120	21	10204.4	337	4	28230.1	124	17	0.36 (0.13, 1.03)	18	10204.4	337	4	33211.0	98	14	0.31 (0.11, 0.84)	3	-	-	0	13224.8	254	3	- (-, -)
MARSTACIMAB	DAY 240	22	13320.9	123	4	32451.6	91	18	0.41 (0.19, 0.89)	19	13320.9	123	4	31470.0	83	15	0.42 (0.20, 0.90)	3	-	-	0	37838.5	175	3	- (-, -)
MARSTACIMAB	DAY 300	22	18486.1	29	4	30391.3	108	18	0.61 (0.28, 1.33)	19	18486.1	29	4	27013.5	106	15	0.68 (0.31, 1.49)	3	-	-	0	54775.9	102	3	- (-, -)
MARSTACIMAB	DAY 360	21	21947.5	146	3	30412.0	97	18	0.72 (0.29, 1.79)	18	21947.5	146	3	31045.6	81	15	0.71 (0.30, 1.65)	3	-	-	0	27432.9	263	3	- (-, -)

Abbreviations: ADA +ve: ADA positive; ADA -ve: ADA negative.
N: Total number of participants in each age group and dose group. N1: Total number of participants in each age group, dose group and analysis visit with non-missing ADA status and having non-zero concentration value.
n: Number of participants in each analysis visit and ADA status group having non-zero concentration value.
GMR :Geometric Mean Ratio CI :Confidence Interval
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 100 ng/mL.
PFIZER CONFIDENTIAL SDTM Creation: 16JUL2025 (05:10) Source Data: adpc Table Generation: 08AUG2025 (08:46)
(Data cutoff date :26MAY2025 Database snapshot date :07JUL2025) Output File: /IACSR2025/B7841008_IA1_CSR/adpc_s001_gmr
Table 14.4.4.1.3a Marstacimab is for Pfizer internal use.

Immunogenicity results for the extension study B7841007

Adults (Parent Study B7841005)

Two (2) out of a total of 116 ADA-evaluable adult participants (with and without inhibitors) had positive ADA titers at baseline. Of the 116 ADA-evaluable adult participants, 7 adult participants (6.0% incidence) were ADA+ve (all were treatment-induced). Out of the 7 ADA+ve participants, 1 (1 out of 28 inhibitor cohort participants; 3.6%) was an inhibitor cohort participant and 6 (6 out of 88 non-inhibitor cohort participants; 6.8%) were non-inhibitor cohort participants. ADA titers were low (maximum titer log10 value = 3.28, titer log10 cut off = 1.53). Out of the 7 ADA+ve participants, 2 (28.6%) were ADA+ve by the first assessed visit at Year 1 Day 180 (both negative at end of parent study). ADAs were transient (ADA positivity for <16 weeks at any time during the study) in 71.4% (5/7), persistent (ADA positivity for ≥16 weeks at any time during the study) in 14.3% (1/7), and indeterminate in 14.3 % (1/7) of the ADA+ve participants, indicative of a transient ADA profile in the majority of the participants. Duration of ADA persistence in the 1 ADA-persistent participant was 715 days and the participant was ADA+ve at his last assessment visit at Year 3 Day 180 (titer log10 of 2.49). No adult participants were NAb+ve in the OLE study.

Adolescents (≥12 - <18 years; Parent Study B7841005)

None of the 30 ADA-evaluable adolescent participants who enrolled from B7841005 had positive ADA titers at baseline. Of the 30 ADA-evaluable adolescent participants, 3 participants (10.0% incidence) were ADA+ve (all were treatment-induced). Out of the 3 ADA+ve participants, 2 (2 out of 12 inhibitor cohort participants; 16.7%) were inhibitor cohort participants and 1 (1 out of 18 non-inhibitor cohort participants; 5.6%) was a non-inhibitor cohort participant. ADA titers were low (maximum titer log10 value = 2.48, titer log10 cut off = 1.53). Out of the 3 ADA+ve participants, 1 (33.3%) was ADA+ve by the first assessed visit at Year 1 Day 180 and 2 were ADA+ve by Year 1 Day 360 (all 3 were ADA-ve at end of parent study). ADAs were transient (ADA positivity for <16 weeks at any time during the study) in 66.7% (2/3) and persistent (ADA positivity for ≥16 weeks at any time during the study) in 33.3% (1/3) of the ADA+ve participants, indicative of a transient ADA profile in the majority of the participants. Duration of ADA persistence in the 1 ADA-persistent participant was 717 days and the participant was ADA+ve at his last assessment visit at Year 3 Day 360 (titer log10 of 2.11) (Note: Since ADA samples were collected every 6 months, it is not possible to truly assess whether ADAs are transient, based on immunogenicity terms and definitions. As such, assignment of transience for ADA should be interpreted in the context of the study design). No adolescent participants who enrolled from B7841005 were NAb+ve in the OLE study.

Adolescents (≥12 - <18 years; Parent Study B7841008)

One (1) out of a total of 17 ADA-evaluable adolescent participants who enrolled from B7841008 had a positive ADA titer at baseline. Of the 17 ADA-evaluable adolescent participants, 1 inhibitor cohort participant (5.9% incidence) was ADA+ve (treatment-induced) at 1 time point (Year 1 Day 360). ADA titer was low (titer log10 value = 1.99, titer log10 cut off = 1.53). This participant could not be classified as transient or persistent since only 1 ADA result was available as of the cut-off date. No adolescent participants who enrolled from B7841008 were NAb+ve in the OLE study.

Overall, ADA incidence in this OLE study (as of the cutoff date of May 30, 2025) was 6% in adults and 6% - 10% in adolescent haemophilia populations with and without inhibitors. In general, marstacimab immunogenicity was of low incidence, low titer, and mostly transient in nature, with 0% incidence of NAb positivity.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology data available at the time of the initial MAA were mostly based on data from haemophilia patients without inhibitors and healthy volunteers. Importantly, the interim CSR of the pivotal phase 3 study B7841005 only included PK/PD data from the non-inhibitor cohort. With this application, the MAH submitted a CSR including data from participants with haemophilia with inhibitors. In addition, PK/PD and immunogenicity data from the paediatric study B7841008 were included in the submission, but only for adolescent haemophilia patients with or without inhibitors, in line with the applied age range. From the extension study B7841007, which includes patients who rolled over from studies B7841005 and B7841008, only immunogenicity data are available. In line with the protocol of study B7841007, no PK and PD evaluations were performed during this study as no participants tested positive for both ADA and NAb.

The clinical summaries and the population PK and PK/PD models were updated with the new data.

Information on the clinical pharmacology data, the mechanism of action, the investigated PK/PD markers in general, and the applied population PK and PK/PD models is available in the European Public Assessment Report (EPAR) for the initial MA of Hympavzi (EMA/464842/2024).

The same fully validated assays as for the initial MAA were used for determination of marstacimab drug concentrations (PK), total plasma TFPI (PD) and detection of ADA and NAb. As previously, the remaining PD parameters (thrombin generation, D-Dimer and prothrombin fragments 1+2) were measured using laboratory developed tests validated under CLIA requirements.

The inhibitor cohort of Study **B7841005** included 51 participants with haemophilia A and B (38 adults and 13 adolescents; 40 Haem A and 11 Haem B) receiving either 150 mg SC QW or 300 mg SC QW marstacimab who had at least one evaluable PK concentration and contributed data for the analyses.

Regarding the paediatric study **B7841008**, at the cutoff date of 26 May 2025, a total of 23 adolescent participants with haemophilia A and B (9 inhibitor cohort participants and 14 non-inhibitor cohort participants) had at least one evaluable PK concentration and contributed data for the analyses.

PK/PD results from Study B7841005

The new **PK** data from participants with inhibitors showed plasma concentrations of marstacimab within a similar range as previously reported and assessed for non-inhibitor patients.

Only few (n=4) participants with inhibitors had a dose escalation to weekly 300 mg SC QW, which led to a more than proportional increase of the plasma marstacimab concentration. This was already

observed for participants without inhibitors. The PK data from participants who had a dose escalation are extremely limited, but the available median plasma levels were within the already known range.

In line with the non-inhibitor population, adolescents with inhibitors had higher median plasma marstacimab concentrations compared to adults with inhibitors. However, weight was identified as an important covariate for parameters such as clearance (Cl) and central volume of distribution (V_c) in both the initial and the updated population PK model. Based on weight-adjusted calculations, the higher concentrations in adolescents could be attributed to the weight differences in the populations. Based on modelling data, the weight-adjusted $C_{avg,ss}$ for a typical adolescent was ~11% higher when compared to the exposure for a typical adult participant. Upon request, the MAH explored potential additional reasons (other than body weight) for differences in exposure levels and identified central volume (Vc) as contributing factor. Vc for a typical adolescent was ~85% of the value for a typical adult. The MAH provided data for an exposure scenario where Vc was kept the same for adult and adolescent participants, but there was a difference in CL, Q and Vp between the 2 populations based on geometric mean differences. In this scenario, exposures were comparable between adolescents and adults.

The population PK analysis suggests a slightly higher mean/median steady state exposure (Cmin, Cmax, Cavg, AUC) to marstacimab in participants with inhibitors compared to those without inhibitors. However, the exposures are within the known ranges and based on the available clinical data (PK/PD with known high variability, efficacy, safety), the potential slight differences between non-inhibitor and inhibitor patients are not expected to be clinically significant. Investigation of population factors such as haemophilia type, race (Asian vs. non-Asian), or mild hepatic or renal impairment did not reveal clinically significant differences in terms of exposure based on the modelling data. The potential impact of elderly age was not studied because of too limited data in this population (n=2 participants ≥65 years of age in the inhibitor cohort).

The median values of the investigated **PD** markers (peak thrombin, PF 1+2, D-dimer, total TFPI, in participants with haemophilia A or B with inhibitors showed similar patterns as previously reported for participant without inhibitors (EPAR, EMA/464842/2024). Depending on the PD marker, steady state was (roughly) reached either at the first post-baseline data point at Day 7 (peak thrombin, PF 1+2, D-dimer) or the second post-baseline data point at Day 60 (total TFPI).

Based on observed data, there was no clinically significant impact of inhibitor status on PD markers, despite lower peak thrombin levels in inhibitor patients at baseline. Also, in line with previous data, adolescent participants with inhibitors had higher median values for total TFPI, D-dimer and a trend for slightly higher values for PF 1+2 compared to adult participants, while median peak thrombin values were lower. The available efficacy and safety data do not suggest a need for dose adjustment in adolescents. Except for a single measurement, peak thrombin values (TGA peak) were below the 97.5th percentile of baseline pre-dose values in healthy volunteers (normal physiological values), which is important to consider with regards to the potential thrombotic risk.

For the few inhibitor participants with dose escalation to 300 mg SC QW (n=3), the observed values of PD markers in inhibitor patients were within known ranges from patients without inhibitors. There was one notable outlier for PF 1+2 but only on Day 60. In the CSR (not shown in this assessment report), the median PF 1+2 value on Day 60 is based on only 2 data points with one value being an order of magnitude higher than usual. It can only be speculated whether this single extraordinarily high PF 1+2 value may have been caused by an error. Considering that all other data points throughout the different sampling time points were within the usual range, no concern was raised in this regard.

In line with previously available data, a high inter and intra patient PK and PD variability was noted. As discussed for the initial MA, potential factors for the observed variability include different sampling time

points (depending on timing of clinical visits), patient weight, and probably also variable soluble and cell surface levels of TFPI.

The MAH was asked whether the increased exposure in patients with inhibitors, especially those treated with 300 mg QW, could increase the risk of thrombosis. The MAH stated that the available clinical data did not demonstrate a concentration-dependent increase in thrombotic risk across the studied exposure range and that there were 2 thrombotic events in 2 patients on a marstacimab dose of 150 mg SC QW across the development program. PK samples were not collected during these safety events, but PK samples collected after the events and during the parent study B7841005 were in line with typical values seen for this dose group. The MAH further argued that PD biomarker levels at both dose levels were within the typical physiological range reported in healthy volunteers.

It is acknowledged that the currently available safety and PD data do not indicate a concern with respect to a potentially increased thrombotic risk in individuals who receive the 300 mg SC QW dose. However, it needs to be pointed out that the clinical database for patients with escalated dose is very limited, particularly in inhibitor patients. Therefore, no clear conclusion can be made with respect to the higher dose level and some uncertainty remains. Importantly, there were three additional thrombotic events (2 events from postmarketing reporting and 1 recent fatal event in the extension study B7841007). All 5 thrombotic events were reported in patients who received the lower dose of 150 mg SC QW. See the safety section for more details. Therefore, the posology section 4.2 of the SmPC was amended to include information for patients on a maintenance dose of 300 mg as well as recommendations on switching from prophylactic factor replacement therapy or bypassing agents to Hympavzi. In addition, warning statements in section 4.4 of the SmPC with regards to thromboembolic was further strengthened, also adding emphasis on patients with a history of thromboembolic events. Please refer to clinical safety section.

PK/PD results from Study B7841008

The exposure and PD data from the new paediatric study B7841008 (only data from adolescents available) were consistent with study B7841005.

One adolescent haemophilia patient with inhibitors who had a dose escalation to 300 mg SC QW showed notably high plasma marstacimab concentrations in the upper range of usually reported values in previous studies, at least for 2 of 3 reported sampling time points (D240, D300). The concentration was decreased at D360. This did translate into higher total TFPI values in this participant. Considering that the peak thrombin, PF 1+2 and D-dimer values were within the expected range, no concern was raised.

Immunogenicity and potential impact of anti-drug antibodies (ADAs) on PK and PD

In Study **B7841005**, the incidence of ADAs (19.6%; 10/51 evaluable participants) in the inhibitor population was very similar to the non-inhibitor population (19.8%; 23/116 evaluable participants). Two out of these 10 ADA positive participants (20%) with inhibitors were also positive for NAbs, compared to 6 out 23 ADA (26.1%) positive participants without inhibitors (see EPAR of the initial MAA). ADAs and NAbs were mostly transient, except for one participant.

The plasma concentrations of marstacimab were slightly lower in ADA positive participants compared to ADA negative participants. This was also observed for patients without inhibitors and reflected in section 5.1 of the SmPC. Considering the wide ranges of observed plasma concentrations between the different participants, slightly decreased levels seem negligible.

In participants with inhibitors, TGA peak levels were slightly but consistently lower in ADA positive vs. ADA negative participants throughout the measured time points. For total TFPI, there was also a trend

for overall slightly lower values in ADA positive participants, at least for most of the relevant time points. In contrast, results from the remaining PD biomarkers (PF 1+2, D-dimer) were inconclusive.

The presence of ADA did not seem to impact efficacy of marstacimab in haemophilia patients with inhibitors.

In adolescent participants of the paediatric Study **B7841008**, the incidence of ADA (16.7%, 4/24 evaluable participants) and NAbs (25%, 1/4 ADA positive participants) were comparable to Study B7841005. The marstacimab concentrations in plasma were lower in ADA positive compared to ADA negative participants but the interpretability is limited based on the low sample size. The study is still ongoing and no PD data by ADA status were available.

In the open label extension Study **B7841007**, the incidence of ADA was slightly lower compared to previous studies (6% in adults and 6% - 10% in adolescent haemophilia populations with and without inhibitors). No adult or adolescent patient was positive for NAbs. No PK/PD data are available from the extension study.

2.3.6. Conclusions on clinical pharmacology

The PK, PD and immunogenicity data from individuals with haemophilia A or B with inhibitors were consistent with previously reported data and did not reveal any new findings, except for a clinically not significant increase in marstacimab-exposure, compared to non-inhibitor patients. Changes have been made to section 4.2, 4.4 and 5.1 respectively.

2.4. Clinical efficacy

Following the initial MAA, Hympavzi (marstacimab or PF-06741086) is approved for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital FVIII deficiency) without FVIII inhibitors or severe haemophilia B (congenital FIX deficiency) without FIX inhibitors.

With this submission, the extension of the indication was intended to include use of marstacimab for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with haemophilia A with FVIII inhibitors or haemophilia B with FIX inhibitors.

The pivotal efficacy and confirmatory evidence supporting the indication expansion in patients ≥12 years of age with inhibitors are derived from the completed inhibitor cohort of the single Phase 3 Study B7841005 and the corresponding OLE study (Study B7841007). The efficacy data from the non-inhibitor population from Studies B7841005 and B7841007 were presented in the initial MAA.

Table 10: Clinical efficacy studies included in the martsacimab type II variation for the proposed indication in participants ≥12 years of age with inhibitors

Study	Description	Population	N (enrolled)	N (SCE clinical efficacy dataset)	Dose(s) / Frequency	Duration	Age (Years)	Study Status
Phase 3 Studies Contributing Efficacy and Safety Data for the Proposed Indication								
B7841005	Phase 3 Pivotal	Severe hemophilia A & moderately severe to severe hemophilia B	Total N = 188 Non-inhibitor cohort[a]: 128/188 Inhibitor cohort: 60/188	Total Inhibitor cohort: 51 Inhibitor cohort with historic on-demand: 48 Inhibitor cohort with historic routine prophylaxis: 3	300 mg loading dose 150 mg /QW[b]	12 months	12 to <75	Non-inhibitor cohort[a]: completed Inhibitor cohort: completed
B7841007	Phase 3 OLE of Study B7841005	Severe hemophilia A & moderately severe to severe hemophilia B	Total N = 155 Non-inhibitor cohort: 108/155 Inhibitor cohort: 47/155	Total Inhibitor cohort[c]: 47 Inhibitor cohort with historic on-demand[c]: 44 Inhibitor cohort with historic routine prophylaxis[c]: 3	150 mg / QW[b]	Up to 43.1 months at time of data cut (in addition to 12 months exposure in Study B7841005)	12 to <75	Non-inhibitor and inhibitor cohorts: ongoing

a. Results from the B7841005 non-inhibitor cohort were presented in the initial MAA submission.
b. Protocol-defined criteria allowed for dose escalation to 300 mg/QW.
c. Inhibitor cohort B7841007 participants enrolled from Parent Study B7841005 inhibitor cohort

2.4.1. Main study

B7841005: Pivotal Phase 3 Study, Inhibitor Cohort

Methods

This was a one-way, cross-over, open-label, multi-center study planned for approximately 145 adolescent and adult participants 12 to <75 years of age with severe haemophilia A or moderately severe to severe haemophilia B (defined as FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitors, with approximately 20% of adolescent participants (12 to <18 years of age). Additional participants (approximately 20%) could have been recruited for this study to account for attrition of enrolled participants and to provide for sufficient representation into regions which have experienced recruitment delays due to the COVID-19 pandemic. This study was comparing treatment

with the participant's prescribed factor replacement therapy or bypass therapy during an OP with a 12-month ATP, during which participants were to receive marstacimab prophylaxis (defined as treatment by SC injection of marstacimab).

The dosing regimen was marstacimab 300 mg SC for the initial loading dose followed by 150 mg SC QW. Individual participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding, may have had their dose increased to 300 mg SC QW.

Participants were to be enrolled into 1 of 2 cohorts:

- **Inhibitor Cohort** – individuals with inhibitors who were receiving prior on-demand treatment (≥45 participants, with at least 35 haemophilia A and 10 haemophilia B participants). Note: A limited number of participants with inhibitors who were receiving prior prophylactic treatment were enrolled and included in the safety evaluation of the inhibitor cohort.
- **Non-Inhibitor Cohort** – 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 inhibitor cohort (n ≥45) was to include at least 5 adolescent participants and the non-inhibitor cohort (n ≥100) was to include at least 20 adolescent participants.

Treatment during the 6-month OP consisted of the following:

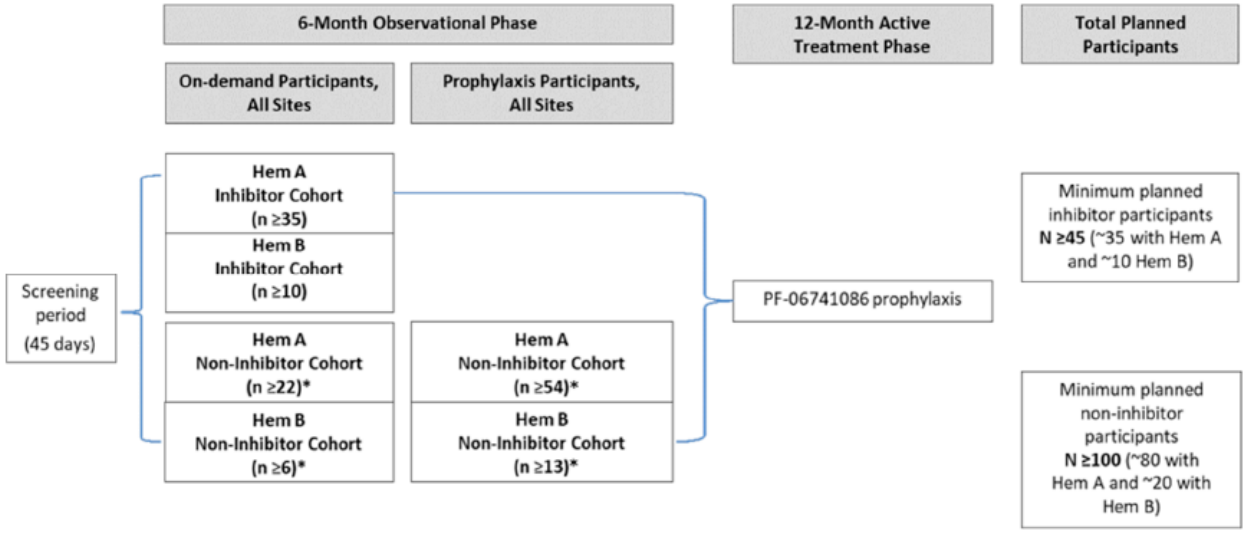
Prior On-Demand Treatment: Participants with either haemophilia A or B, with or without inhibitors, and who were prescribed an on-demand treatment regimen during the OP, transitioned to the ATP after 6 months. Participants with inhibitors received on-demand treatment with rFVIIa, PCC, or aPCC agents, e.g., FEIBA or in regions where available, BYCLOT, and participants without inhibitors were to receive on-demand treatment with FVIII- or FIX-replacement therapy during the OP before crossing over to the 12-month ATP.

Prior Prophylaxis Treatment: Participants without inhibitors who were on prior prophylactic treatment with FVIII- or FIX-replacement during the OP transitioned to the ATP after 6 months.

The study duration for an individual participant was approximately 21 months, including an approximately 45-day screening period, an OP of 6 months, a 12-month ATP during which the participant was to receive an initial loading dose followed by prophylaxis treatment with marstacimab, and a 1-month follow-up for safety monitoring.

The overall study schematic is provided below in Figure 21.

Figure 21: Study schematic



*Remaining 5 participants will be allocated to the non-inhibitor cohorts at the discretion of the sponsor.
Note: Participants with FVIII or FIX inhibitors who are treated with routine prophylaxis may be enrolled, on a case-by-case basis (to supplement the safety analysis of the inhibitor cohorts) after discussion and agreement from the Pfizer medical monitor.

Study participants

Enrolled in this study were adult or adolescent male participants (12 to <75 years of age) with a diagnosis of severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) who consented to participate in the study. Inclusion criteria for the inhibitor cohort are detailed below.

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

- Participant must be male and 12 to <75 years of age with a minimum body weight of 35 kg at the time of signing the informed consent.

Type of Participant and Disease Characteristics

- Participants with a diagnosis of severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) documented by a clinical laboratory prior to Enrolment. The severity of haemophilia may be confirmed either by documented historical evidence from a clinical laboratory prior to Screening or by factor activity obtained from a clinical laboratory (which may include the central laboratory for this study) prior to Enrolment.
- Participants who are enrolled into the **Inhibitor Cohort** must also meet the following criteria:
    - Documentation of current high titre inhibitor (≥5 BU/mL); or current low titre 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 Enrolment into Observational Phase.

- Participants who have documented inhibitors while on factor-replacement therapy but who do not meet the quantitative inhibitor criteria described in the prior bullet at the time of Screening (e.g., participant with a previously documented high-titer inhibitor (≥5 BU/mL) and whose condition precludes re-challenge with FVIII or FIX replacement) may be considered for eligibility on a case-by-case basis with discussion and agreement from the Pfizer medical monitor.
- Haemophilia A participants with on-demand treatment regimen with ≥6 bleeding episodes or haemophilia B participants with ≥4 bleeding episodes (spontaneous or traumatic) necessitating treatment with bypass factor during the 6 months prior to Enrolment into Observational Phase and willing to continue to receive on-demand treatment during the Observational Phase. Surgical bleeding episodes do not apply to this criterion.
- 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 demonstrated at least 80% compliance with scheduled prophylaxis regimen during the 6 months prior to enrolment, may be considered for eligibility on a case-by-case basis with discussion and agreement from the Pfizer medical monitor.

Sex

- Male

Informed Consent

- Participant or legally authorized representative, or participant's caregiver capable of giving signed informed consent (or minor assent, when applicable) as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent document (ICD) and in this protocol.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

- Previous or current treatment for or history of coronary artery diseases, venous or arterial thrombosis (Common Terminology Criteria for Adverse Events [CTCAE]14 Grade >1), or ischemic disease (except for catheter-associated thrombosis).
- Known planned surgical procedure during the planned study period.
- Known haemostatic defect other than haemophilia A or B.
- Abnormal renal or hepatic function as defined by the following laboratory results at Screening:
  - Alanine transaminase (ALT) >2 × upper limit of normal (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, hypalbuminaemia, 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 -e.g., 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

- Serum albumin less than the lower limit of normal (LLN).
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2.

- Abnormal heamatology values as defined by the following laboratory tests at Screening:
  - Platelet count <100,000/uL
  - Hemoglobin level <10 g/dL
- Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behaviour 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.
- Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.

Prior/Concomitant Therapy

- Current routine prophylaxis with bypassing agent (e.g., aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), non-coagulation non-factor replacement therapy (e.g., 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 (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.
- Regular, concomitant therapy with immunomodulatory drugs (e.g., 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 to 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.

Treatments

Description of trial intervention

The study intervention marstacimab (PF-06741086) was administered as 300 mg SC (2 × 150 mg SC injections) for the initial loading dose followed by a single 150 mg SC QW injection via PFS. Individual participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding may have had their dose increased to 300 mg SC QW at any time after completion of ATP Day 180 (Visit 14). All participants were provided the PFS for administration of marstacimab in the study.

Modification of study intervention dose was not required but, under certain circumstances, was allowed. Any decisions related to dose modification due to meeting bleed event criteria will exclude any bleeding data from the first 72 hours of a 300-mg loading dose with study intervention.

Following 6 months of active treatment with PF-06741086, and at any time after completion of Visit 14 (Active Treatment Phase Day 180), the dose may be escalated from 150 mg SC QW to 300 mg SC QW if the following criterion is met and following discussion with the medical monitor:

- The participant must weigh at least 50 kg in order to escalate to the 300 mg SC QW dose. Any participant weighing between 35 kg and <50 kg, including adolescents, must remain on the 150 mg dose.
- **Inhibitor Cohort:** Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of Novo seven FEIBA or in regions where available, BYCLOT over a 6-month period.

Significant spontaneous bleeds were defined as those that lead to a transient or persistent loss of function. The loss of function may be transient and may evidence itself by a reluctance of the participant to utilize the affected body part in usual activities be it on account of pain, associated swelling or limitation in motion. This specification was intended to prevent regimen escalation based upon clinically insignificant or minor bleeding episodes (e.g., ecchymoses, epistaxis).

Concomitant and rescue therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, or herbal supplements) that the participant is receiving at the time of Screening or receives during the study had to be recorded along with reason for use, dates of administration including start and end dates, and dosage information including dose and frequency. The medical monitor was to be contacted if there were any questions regarding concomitant or prior therapy. In case a participant was scheduled to undergo a surgical procedure, the investigator was to contact the medical monitor and discuss further participation for the participant, as well as any other action which may be required.

Permitted Haemostatic Medication

Haemostatic medication allowed for use during the study is presented in the table below.

Table 11: Permitted haemostatic medications

Cohort	Allowed During Observational Phase		Allowed During Active Treatment Phase
Duration	6 Months		12 Months
Non-Inhibitor	Washout 3-4 days prior to factor activity on Day 1[a]	FVIII, FIX On-Demand, preventative[d], or Prophylaxis (prophylaxis treatments are permitted until initiation of treatment with study intervention)	**PF-06741086 Prophylaxis**[b,c] Breakthrough bleeding: FVIII or FIX, at minimum effective dose according to product label; *Also refer to Prohibited Medications in Section 6.5.2*
Inhibitor	Washout 3-4 days prior to factor activity on Day 1[a]	rFVIIa, PCC, aPCC including FEIBA, or BYCLOT On-Demand, or preventative[d] • When agreed between investigator and Pfizer medical monitor, current routine prophylaxis with bypassing agent (eg, rFVIIa, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC]) (prophylaxis treatments are permitted until initiation of treatment with study intervention)	**PF-06741086 Prophylaxis**[b,c] Breakthrough bleeding: • rFVIIa (≤90 µg/kg approx. every 2 hours), • or FEIBA at the lowest effective dose, in accordance with the Product Prescribing Information, but should not exceed 100 units per kg per 24 hrs, • or treatment with BYCLOT (in regions where available), in accordance with approved product labeling may be allowed per the specifications in Section 6.5.3 Treatment of Breakthrough Bleeding, • or aPCC or PCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information. *Also refer to Prohibited Medications in* Section 6.5.2

a. Duration of washout of participant's prior haemophilia treatment prior to factor activity laboratory assessments is dependent upon prior treatment as follows:
- From FVIII replacement therapy for at least 72 hours;
- From extended half-life FVIII replacement therapy for at least 4 × half-life;
- From FIX replacement therapy for at least 96 hours;
- From extended half-life FIX replacement therapy for at least 4 × half-life;
- From bypass agent therapy (either rFVIIa, PCC, aPCC, FEIBA, or BYCLOT) for at least 72 hours.

Note: If a participant experiences an acute bleeding episode during this washout period requiring treatment with a FVIII or FIX replacement therapy, or bypass agent therapy, the participant is to be stabilized utilizing this regimen and a new washout period should be initiated.

b. If a participant required a change of factor-replacement treatment regimen during the Observational Phase, the participant will be discontinued. These participants may be screened again, at the discretion of the investigator.

c. Systemic antifibrinolytic agents or medications known to influence platelet function (eg, aspirin or certain non-steroidal anti-inflammatory drugs) washout of ≥120 hours prior to administration of study intervention on Day 0 through completion of ATP Day 360 (Visit 20) in the Active Treatment Phase.

d. Preventative treatments prior to planned activity (eg, sports participation, physical therapy, surgical/medical procedure, etc) should only be given/prescribed to participants after the investigator has discussed these planned treatments with the medical monitor. Agreement of planned preventative treatment/prescription between investigator and medical monitor will be documented. Reasons for preventative treatment will be categorized as either*: a) Medical/Dental procedure; or b) Other.*

Prohibited Medications

Observation and Active Treatment Phases

Throughout all phases of the study, the following medications were prohibited: immunomodulatory medications (e.g., IVIG, routine systemic corticosteroids, rituximab) and

emicizumab. Bypassing agent therapy is not permitted at any time for the Non-Inhibitor Cohort.

Systemic antifibrinolytic agents or medications known to influence platelet function (e.g., aspirin or certain non-steroidal anti-inflammatory drugs) require a washout of ≥120 hours prior to administration of study intervention on Day 0 through completion of ATP Day 360 (Visit 20) in the Active Treatment Phase. Use of these medications is permitted thereafter and other times during the study period.

Active Treatment Phase

The following therapies are prohibited during the Active Treatment Phase unless required for the 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).
    - Prophylaxis treatments with regularly prescribed haemostatic medication are permitted until initiation of treatment with study intervention at Visit 7.
- Inhibitor Cohort: Prophylaxis, on-demand, or preventative treatment with FVIII- or FIX-replacement. Prophylaxis treatment with bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).
    - When agreed between investigator and Pfizer medical monitor, current routine prophylaxis with bypassing agent are permitted until initiation of treatment with study intervention at Visit 7.

Treatment of Breakthrough Bleeding

For inhibitor participants who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or treating physician requires additional haemostatic therapy beyond PF-06741086 prophylaxis, rFVIIa, PCC, aPCC, FEIBA, or BYCLOT (in regions where available) are allowable.

- FEIBA may be administered at the lowest effective dose, in accordance with the Product Prescribing Information but should not exceed 100 units per kg per 24 hours.
- PCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information.
- aPCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information.
- rFVIIa may be administered at the lowest effective dose but not to exceed 90 µg/kg per dose and not to exceed a dosing frequency of approximately every 2 hours *(for Japan country changes refer to Appendix 7: Country- specific requirements).*
    - If a participant receives treatment with rFVIIa at a dose >90 µg/kg or is receiving treatment with rFVIIa more frequently than approximately every 2 hours, the investigator must immediately contact the sponsor's medical monitor to discuss the case. A determination will be made at that time if the participant should continue to receive PF-06741086, remain in the study, or be withdrawn from further participation.

- Treatment with BYCLOT (in regions where available), in accordance with approved product labelling may be allowed only in the following scenarios in cases where such treatment is considered medically necessary during an emergency situation:
    - rFVIIa provides insufficient control of participant's bleeding;
    - In the absence of other suitable haemostatic medication.
    - In such cases, the investigator then must contact the sponsor's medical monitor to develop a treatment plan for administration of BYCLOT. In the event an emergent treatment with BYCLOT is required before a contact with the sponsor's medical monitor is feasible, it is important for the treating physician to contact the medical monitor as soon as possible.
    - The allowance of BYCLOT, the precise dose, and the frequency must be clearly documented in the source documentation and case report form (CRF). In case an agreement is not reached between the investigator and medical monitor, the participant must be discontinued from any further treatment with PF-06741086.

Pausing or withdrawal of treatment with PF-06741086 is not required in the event of a breakthrough bleed but may be considered at the discretion of the investigator.

All bleeding episodes and products used for treatment of these bleeding episodes must be recorded in the participant's diary.

Study assessments

Bleeding episodes were evaluated as described in the following subheadings. The information regarding occurrence of bleeding episodes, including IV treatments with coagulation factor products or bypass agents, was collected via participant diaries and medical records.

Joint assessments were performed using the HJHS Version 2.1 to evaluate joint total and global gait scores. Patient-reported outcomes were collected using 2 types of electronic devices; a handheld device and a site tablet device. The handheld device was used as a diary to continually collect data on marstacimab dosing, bleeds, and non-study intervention infusions while the site tablet was used to collect data on all other PRO measures. PRO assessments included the EQ-5D-5L, the Haem-A-QoL (≥17 years of age) and Haemo-QoL (12 to <17 years of age), the HAL (≥17 years of age) and pedHAL (12 to <17 years of age), the PGIC-H, and the HLIQ.

Haemophilic Bleeding Episodes

During this study, the investigator (or qualified designee) reviewed the participant diary with the participant, and inquired about and recorded AEs, concomitant therapy, bleeding episodes (including location and aetiology – traumatic or spontaneous), and any haemostatic treatments (including IV treatments with coagulation factor products or bypass agents).

Haemostatic therapy administered to treat bleeding episodes during the Screening period and during the Observational and Active Treatment Phases through the final study visit was to be documented as concomitant therapy. Participant diary review included any bleeding episodes experienced during participation in this study. Bleeding episodes requiring treatment with IV coagulation factor products or bypass agents counted toward the determination of bleeding episode frequency for the primary efficacy endpoint. Data on the participant diary was to be reviewed by the investigator at study visits. Any eDiary noncompliance was to be reported to the sponsor.

Bleeding

Occurrences of bleeding episodes were to be obtained from participant diaries and medical records. Where relevant, investigators (or qualified designee) and monitors were to ensure consistency between the participant's medical record or participant diaries and the AE CRFs, as applicable. Bleeding episodes which were related to the participant's haemophilia were not to be reported as AEs unless associated with a SAE, although the concomitant events associated with a bleed may be reported as an AE if appropriate. Both spontaneous bleeding episodes and traumatic bleeding episodes were collected. Only bleeding episodes considered not related to the participant's haemophilia, or if the bleeding episodes were considered serious and met the SAE criteria should be listed on the AE CRF page. When bleeding episodes that meet the SAE criteria were recorded on the AE CRF, the location (site) of the bleed and the etiologic classification as spontaneous or traumatic should be included. The participant diary or medical record served as the source document for bleeding episodes during the study. Investigators (or designee) reviewed the participant's diary/medical records to assist in classification if necessary.

Types of Bleeding

For the purposes of this study, a bleed was classified as either spontaneous or traumatic. The criteria for spontaneous and traumatic bleeds are described below.

Spontaneous Bleeding Episodes: Bleeding episodes should be classified as spontaneous if a participant records a bleeding event when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity, or "overuse". The determination of "strenuous" or "overuse" is at the discretion of the participant/caregiver/investigator. For example, if a participant were to wake up in the morning and note he was bleeding, a "spontaneous" bleed would be recorded. Target joints can have spontaneous bleeding episodes.

Traumatic Bleeding Episodes: Bleeding episodes should be classified as traumatic if a participant records a bleeding event when there is a known or presumed contributing factor/reason for the bleed. For example, if a participant were to exercise "strenuously" and then have a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed. Target joint bleeding episodes can be traumatic if a known action led to bleeding into the joint.

Location of Bleeds

For the purposes of this study, when participants report a bleed, the location of the bleed should be recorded in the participant's eDiary. In rare cases, when the eDiary is not available such as an emergency situation or hospitalization, bleeds may be recorded in the participant's medical records. Bleeds were to be reported as occurring in 1 of the following locations: joint, muscle/soft tissue, or other. Each individual location of multiple site bleeds was to be reported. For joint bleeds, the specific joint was to be reported. Parameters to identify joint bleeds include: pain on joint motion, limitation of motion, and visible swelling of joint.

Treatment of Bleeding Episodes

Bleeding episodes that occur during this study may be treated (on-demand) with haemostatic therapy (e.g., IV coagulation factor products or rFVIIa bypass agent therapy at approximately 90 µg/kg) as deemed appropriate by the investigator. The specific treatment with haemostatic therapy is at the discretion of the participant/caregiver/investigator, but all doses of haemostatic therapy taken after signing of informed consent will be documented as concomitant medications or concomitant therapy.

If a participant experienced a bleeding episode during the washout period preceding screening laboratory assessments, the participant was to be stabilized utilizing the participant's usual haemostatic treatment regimen. Once the bleeding episode has been successfully treated a new washout period should be completed prior to obtaining the screening laboratory tests.

If a participant experienced a bleeding episode during the washout period preceding collection of the FVIII or FIX activity sample collection at Visit 7 (Active Treatment Phase Day 0 Pre-Dose visit), the participant was to be stabilized utilizing the participant's usual haemostatic treatment regimen and a new washout period should be implemented. Once treatment of the bleeding episode with haemostatic agents has been completed a new washout period should be initiated in anticipation of the initial treatment with PF-06741086.

Haemophilia Joint Health Score (HJHS)

Joint assessments will be performed using the Haemophilia Joint Health Score (HJHS) 2.1 during the Observational Phase, in order to establish a baseline assessment for later comparison, and during the Active Treatment Phase to evaluate joint total (swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and strength) and global gait scores. The HJHS is designed for use by physiotherapists. In order to maintain precision and validity of the tool (score), the developers strongly recommend that the tool be used by physiotherapists/healthcare professionals who have haemophilia-related expertise/experience and have been trained in the use of clinical measures, musculoskeletal assessments and specifically administration of the HJHS. Training on use of the HJHS assessment tools was provided and had to be completed by the designee(s) performing these assessments.

Definitions for bleeding events used in the study

Bleed: A bleed is classified in this study as either "spontaneous" or "traumatic". Any sign or symptom of a bleed, regardless of whether or not medication/treatment is administered, should be reported as a "bleed" or "bleeding episode".

Treated Bleed: If a bleed is treated with factor replacement or bypass agents within 48 hours of start of bleeding, regardless of the type of treatment (preventive, prophylaxis or on- demand medication), it would be considered as a treated bleed.

New Treated Bleed: A treated bleed from the same location occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated or a treated bleed occurring at a different site regardless of the time of the bleed.

New Untreated Bleed: An untreated bleed is considered a "new untreated bleed" if occurring >48 hours after the previous untreated bleed at the same site or occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated; an untreated bleed occurring at a different site is considered a "new untreated bleed" regardless of the time of the bleed.

Definitions of bleed sites

Target Joint: Defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6-month period).

Joint Bleed: A bleeding episode characterized by rapid loss of range of motion as compared with baseline that is associated with any combination of the following: pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint.

Muscle Bleed: An episode of bleeding into a muscle, determined clinically or by imaging studies, generally associated with pain or swelling and functional impairment.

Patient-Reported Outcomes

Patient-reported data were collected using 2 types of electronic devices, a handheld device similar to a cell phone and a site tablet device. The handheld device was used as a diary to continuously collect data on bleeds and non-study intervention infusions. The site tablet was used to collect data on all other patient reported outcome (PRO) measures. In the event the electronic devices were not available, paper versions could be used during the Observational Phase for the initial visits.

Data on bleed, non-study intervention infusion, study intervention injections, and any exogenous factor replacement or bypass therapy were collected continuously by the participant or a caregiver using an electronically administered bleed and infusion diary on a handheld provisioned device.

Data on participant health status and health-related quality of life (HRQoL) was collected at scheduled office visits using an electronic device (tablet) provided to each site.

Participant entries were date- and time-stamped to ensure the integrity of the data. A reminder alarm was programmed for a time selected by the participant upon enrolment for their scheduled injections of study intervention.

Data obtained throughout this period was downloaded from the electronic device into the Pfizer electronic PRO (ePRO) vendor's database automatically in real time upon completion of the diary by the participant.

The investigator (or designee) had to inform the participants of the data entry schedule expected of them. The investigator (or designee) was responsible for regular monitoring of the compliance of the participants via the ePRO vendor's web portal. The ePRO system automatically notified the investigator and designated site staff when data were not recorded on the ePRO server on the required schedule.

ePRO System (PRO and eDiary) Training and Use

Training materials and user guides was provided to the study site staff and the participants. Before being allowed to enter clinical data into the eDiary or tablet devices, each user had to be trained in use of the system and their responsibilities for data entry. Each participant allowed to enter participant data had to select a Personal Identification Number (PIN) that had to be kept private. Data could not be entered without first entering the unique PIN or password. The system authenticated the identity of the user. All users had to be trained that passwords and PIN codes are not to be shared. The study site allowed access to view data on the ePRO System to authorized regulatory personnel or sponsor auditors to the extent possible and in conformance with information in the investigator Initiation Package.

Patient Reported Outcomes (PROs) Assessments

PROs were to be completed at the scheduled office visits. An electronic tablet (PRO Tablet) was provided at each site and pre-loaded with the 5 instruments (detailed below). Sites enrolled each participant at the beginning of the study and participants were instructed on the proper use of the device to record their responses. Participants should complete the PROs prior to any of the other scheduled activities on the indicated study days: Observational Phase (OP) Baseline (Visit 2), ATP Visits 6, 7, 10, 12, 14, 16, and 20 (end of treatment or early termination).

Included in the PRO array of measures are the following:

- EuroQoL 5 Dimensions (EQ-5D) 5 Level

Developed by the EuroQoL Group, the EQ-5D is considered the premier measure of health status used in the assessment of the Quality Adjusted Life Year. It measures 5 dimensions of health on a 5-point (5L) scale including Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Also

included is a visual analogue scale anchored by worst and best imaginable health on a 0 to 100 scale where participants are asked to indicate where on the scale they rate their current health.

- Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) and for Children (Haemo-QoL)

The Haem-A-QoL and Haemo-QoL are disease specific measures of health-related QoL in participants with haemophilia, depending on the age of the participant. The Haem-A-QoL is for participants aged 17 years and older and the Haemo-QoL is for participants aged 12 to <17 years. The adult version has 10 domains consisting of 46 items. The 10 domains and the number of items within each domain of the adult version are the following: Physical health (5); Feelings (4); View of yourself (5); Sports and leisure (5); Work and school (4); Dealing with haemophilia (3); Treatment (8); Future (5); Family planning (4); and Partnership and sexuality (3). The adolescent version has 12 domains consisting of 77 items. The 12 domains and the number of items within each domain of the adolescent version are the following: Physical health (7); Feelings (8); Attitude/View (10); Family (8); Friends (4); Other People (6); Sport & School (9); Coping/Dealing (7); Treatment (8); Perceived Support (4); Future (4); and Relationship (2). Scores can be calculated by domain and a single total score, lower score indicates better HRQoL.

- HAL and pedHAL

The Haemophilia Activities List (HAL), version 2 and Paediatric Haemophilia Activities list (pedHAL) are disease specific measures of HRQoL in participants with haemophilia, depending on the age of the participant. The HAL is for a participant aged 17 years and older and the pedHAL is for a participant aged 12 to <17 years. The Haemophilia Activities List (version 2) is a multiple domain measure of the impact of haemophilia on functional abilities in adults. The 7 domains of this instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8); lower (leg) functioning (9); upper (arm) functioning (4); Transportation (3); Self-care (5); Household tasks (6); and Sports/Leisure (7). Scoring can be done by domain, components (Activities involving the Upper Extremities, Basic activities involving the Lower Extremities and Complex activities involving the Lower Extremities) or a standardized total score. The pedHAL is a multiple domain measure of impact of haemophilia on functional capabilities in children. The 7 domains (and respective items) are Sitting/kneeling/standing (10); Functions of the legs (11); Functions of the arms (6); Use of transportation (3); Self-care (9); Household task (3); Leisure activities & sports (11). Scores are calculated by domain and as a sum score.

In the study, HAL was used for participants aged 17 years and older, while pedHAL was used for participants aged 12 to 16 years, in order to match the age cut-offs for Haem-A-QoL and Haem-QoL.

- Patient Global Impression of Change – Haemophilia (PGIC-H)

The Patient Global Impression of Change - Haemophilia (PGIC-H) is a single item assessment of the participant's overall impression of change in their life with haemophilia during the distinct phases of Study B7841005 (i.e., since being enrolled in the study [PGIC-H Observational Phase] and since being infused/injected with PF-06741086 [PGIC-H Active Treatment Phase]). The recall period for the PGIC-H is reflective of the study phase (i.e., "since the start of the study" or "since the infusion received as part of this study". The response scale is a 7-point categorical response scale centered around 'no change' with grades of improvement and 3 grades of worsening.

- HLIQ (Exploratory)

The Haemophilia Life Impacts Questionnaire (HLIQ) is a 9-item assessment of life impacts associated with living with and treating haemophilia. The HLIQ employs a 'past week' recall period. Four items are assessed on a 5-point, ordinal, verbal rating scale (VRS) scored from 0 to 4, while 4 items are gated such that responding 'yes' branches to a 5-point, ordinal VRS and responding 'no' branches to a reason for not participating in the activity, i.e., due to haemophilia or due to other reasons. One item is assessed on a 4-point, ordinal, VRS scored from 0 to 3. Higher scores on the VRSs indicate greater impact due to living with or treating haemophilia.

Objectives

Table 12: Estimands for primary objective

Population	Adult and adolescent patients (12 to <75 years of age) with severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) with inhibitors.
Treatment condition	PF-06741086 for routine prophylaxis during 12-month Active Treatment Phase (ATP) compared to 6-month Observational Phase (OP), regardless of receiving rescue medication in the form of factor replacement or bypass therapy.
Endpoint (variable)	Annualised bleeding rate (ABR) of treated bleeding events
Population-level summary	Mean ABR ratio (marstacimab prophylaxis vs prior on-demand treatment)
Intercurrent events and strategy to handle them	
Receiving rescue medication in the form of factor replacement or bypass therapy	Treatment policy (data during rescue medication will be included)
Preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours), or dose modification and/or discontinuation of treatment	While-on-treatment (data during these intercurrent events will not be included)

The primary objective is addressed via the primary endpoint of ABR of treated bleeds. For the Inhibitor Cohort (participants with on-demand therapy), the ratio of ABR is estimated for the PF-06741086 prophylaxis for the 12-month Active Treatment Phase during Active Treatment Phase over the on-demand treatment during the Observational Phase.

The analyses include those participants who receive at least 1 dose of PF-06741086 prophylaxis after completing the Observational Phase. The ABR for each participant is derived based on the number of treated bleeding events; during the 12-month Active Treatment Phase for PF-06741086 prophylaxis and during the Observational Phase for the respective control group.

With an anticipated trial completion rate of 90%, the derived ABR is expected to closely represent the entire duration of the Observational Phase and the Active Treatment Phase with a minimal rate (<10%) of missing endpoints. Missing values will not be imputed in the primary efficacy analysis. Furthermore, the ABR is derived without regard to the administration of rescue medication use (in the form of coagulation factor replacement or bypass therapy) while any bleeding events after dose increase of PF-06741086 during PF-06741086 prophylaxis are excluded to avoid an inflated efficacy estimate for the 150 mg QW dose of PF-06741086. All data during the preventative medical/dental treatment (plus 72 hours) are also excluded. Rescue medication use is assessed directly via a secondary endpoint of total coagulation factor or bypass product consumption.

Estimands for the secondary objectives

For incidences of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds, the estimand will utilize the same population summary and intercurrent event handling as in the primary endpoint.

For HJHS, the difference in mean changes from baseline at 6 months between the marstacimab prophylaxis in ATP versus the respective reference therapy in OP will be presented using the data irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures. Observations after discontinuation of treatment, if collected, will not be included.

The estimand for all HRQoL endpoints will utilize the same population summary and intercurrent event handling as in the HJHS.

Outcomes/endpoints

Primary objective:

The primary objective of this study was to demonstrate the efficacy and safety of PF-06741086 for routine prophylaxis in severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) participants 12 to <75 years of age with or without inhibitors.

Inhibitor Cohort

For the inhibitor Cohort (participants with prior on-demand therapy), the statistical hypothesis was the demonstration of *superiority* of PF-06741086 prophylaxis observed over a 12-month Active Treatment Phase relative to *on-demand* treatment during the 6 months prior to receiving study intervention, on the ratio of the ABR of treated bleeds using a repeated measures model to account for participant's experience in the OP and ATP, in participants ≥12 years of age with severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) *with inhibitors* who receive *on-demand* treatment during the 6 months prior to receiving study intervention. Superiority was to be declared if PF-06741086 prophylaxis reduced the ABR compared to *on-demand* treatment by at least 50%, i.e., the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) is below 0.5.

Participants with inhibitors who are on routine *prophylaxis* (defined as treatment by IV injection of bypass factor to prevent bleeding) could be enrolled to supplement the safety evaluation of inhibitor

cohort. The efficacy of these participants, if included, were to be separately summarized using descriptive statistics without any hypothesis testing or inferential statistics.

Secondary objectives

Additional efficacy evaluation of PF-06741086

For the inhibitor cohort, the following parameters were assessed for comparison between PF-0674108 prophylaxis observed over the 12-month Active Treatment Phase versus prior on-demand therapy.

- Incidence of joint bleeds
- Incidence of spontaneous bleeds
- Incidence of target joint bleeds
- Incidence of total bleeds (treated and untreated)
- Change in joints as measured by the Haemophilia Joint Health Score (HJHS)

Evaluation of the effect of PF-06741086 on health-related quality of life (HRQoL)

- Haemophilia Quality of Life Questionnaire for Adults (Haem- A-QoL) (≥17 years of age)/Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL); (Adolescents 12 to <17 years of age);
- Haemophilia Activities List (HAL) (Adult ≥17 years of age)/Paediatric Haemophilia Activities List (pedHAL) (Adolescents 12 to <17 years of age)
- Patient Global Impression of Change – Haemophilia (PGIC-H) (Observational Phase and Active Treatment Phase)
- Health Utilities Measure (EuroQol 5 Dimensions 5 Level [EQ-5D-5L])

Sample size

Enough participants were screened to achieve at least 145 participants dosed with PF-06741086. Of these, 45 participants were dosed with PF-06741086 prophylaxis in the On-Demand Inhibitor Cohort; at least 100 participants were dosed in the Non-Inhibitor Cohort (with at least 67 of these participants receiving routine prophylaxis during the Observational Phase and at least 28 receiving on-demand during the Observational Phase).

These 145 participants would ensure sufficient power for the primary endpoint (as described below) and allow an adequate assessment of safety in all cohorts. Over-enrolment by approximately 20% (up to 174 participants) was planned to account for attrition of enrolled participants and to provide for sufficient representation into regions which have experienced recruitment delays due to the COVID-19 pandemic. Finally, participants with inhibitors receiving prior routine prophylaxis may also be allowed to enrol to supplement the safety evaluation of the inhibitor cohort; these participants were included within this 20% over-enrolment group.

For the Inhibitor Cohort (participants with on-demand therapy) in all regions, a sample size of 25 evaluable participants was projected to have ≥90% power (two-sided test with α=0.05) to demonstrate superiority of PF-06741086 prophylaxis in ABR ratio of treated bleeds compared to the on-demand treatment. Superiority was declared if the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) lied below 0.5 using a repeated negative binomial model with log link function. The assumed mean number of bleeds was in the range of 12.5-15 over the 6 months for on-demand treatment and 4 over the 12 months for PF-06741086

prophylaxis with variances assumed as 6 times mean for both treatments. The correlation between the two bleeding count observations from the same participant was assumed to be 0.2.

Randomisation

This was an open-label study; however, the specific cohort assignment to which a participant was assigned was to be reported using An Interactive Voice Response System (IVRS)/ An Interactive Web Response System (IWRS). The site was to contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site was to record the cohort assignment on the applicable CRF, if required.

Blinding (masking)

This was an open-label study.

Statistical methods

Planned analyses

For purposes of efficacy analyses, a modified Intent-to-Treat (mITT) Population was defined including all participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors treated with routine prophylaxis in the OP). With the sixth protocol amendment it was clarified that participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing were to be excluded from mITT and that participants who changed from an inhibitor to a non-inhibitor were to be included in the mITT and considered as inhibitors.

The "All Safety" Analysis Set was to be used in certain sensitivity analyses and included all participants who received at least 1 prophylaxis treatment at OP. Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing were to be excluded from this population. For the Inhibitor Cohort, the primary analysis was planned to estimate the ABR ratio of PF-06741086 prophylaxis over the routine on-demand treatment. A repeated measure negative binomial model via generalized estimating equation (GEE) approach with log link (within-participant comparison) was to be utilized using the number of bleeds requiring treatments as a response variable and treatment (PF-06741086 prophylaxis or routine on-demand) as a factor. The time in treatment was planned to be included as offset variable to account for different follow-up on treatment. Superiority of PF-06741086 prophylaxis was considered demonstrated if the two-sided 95% CI for the ABR ratio (PF- 06741086 prophylaxis/routine on-demand) lay below the pre-set threshold of 0.5. The analysis was to be based on dosed population, and missing values were not to be imputed. The bleeding counts in the analysis also were to include observations during the rescue medication use (in the form of coagulation factor replacement or bypass therapy) but to exclude observations after dose increase during PF-06741086 prophylaxis. All data during the preventative medical/dental treatment (plus 72 hours) were to be excluded.

Supplementary analyses

Supplementary analyses were planned to use the same methodology and summary as the main analysis but were to use the following approaches after the intercurrent events of study drug dose increase or discontinuation.

1. To assess the impact of preventative treatment for medical/dental procedures, sport activity or physical therapy (plus 72 hours): include data

2. To assess the impact of PF-06741086 dose increase, the main analysis was to be repeated with the same model, using the following approaches:

    a) Including data after a dose increase

    b) Imputing the portion after a dose increase using the data before the dose increase to give full weight in the negative binomial regression to the observations from participants with such treatment

    c) Tipping point analysis using ABRs calculated combining bleeds during the intervention dose and assuming the bleed rate after the dose increases as multiples of successively larger (>1) factors of the former to determine the tipping point.

3. To assess the impact of treatment discontinuation, the main analysis was to be repeated with the same model, using the following approaches:

    a) Imputing the portion after treatment discontinuation using the data during treatment to give full weight in the negative binomial regression to the observations from those participants.

    b) Tipping point analysis using ABRs calculated combining bleeds during the treatment and assuming the bleed rate after the treatment discontinuation as multiples of successively larger (>1) factors of the former to determine the tipping point.

Sensitivity Analysis

1. The following analyses were planned to assess the impact of carryover effect from the OP.

    a. The main analysis was to be repeated with the same model, excluding the first month data after initiation of PF-06741086.

    b. Bleed rates during the early part of the treatment period (Months 1-6 in ATP) and the latter part of the treatment period (Months 7-12 ATP) was to be descriptively summarised and compared.

2. The following analysis were planned to be performed to assess the seasonal effect on bleeding; it was planned to use the same methodology and summary as the main analysis but was to include only the observations that match the calendar time between OP and ATP.

Analyses of secondary endpoints

According to version two of the protocol, the following analyses of secondary endpoints were planned:

The bleeding incidence endpoints incidence of joint bleeds; incidence of spontaneous bleeds; incidence of target joint bleeds; and the incidence of total bleeds (treated and untreated) were to be analysed using the same repeated measure negative binomial model via GEE as in the primary analysis, and treatment effect expressed as the ratio of bleeding event rates.

Percentage of participants with no treated bleeding episodes were to be analysed using a McNemar's test to test the null hypothesis that the 2 treatments (PF-06741086 prophylaxis and the routine on-demand) are equivalent. Treatment effect was to be expressed as the difference in percentages. This analysis was later removed from the protocol.

The Total Factor/bypass product consumption as measured in total IU and IU/kg per month and per year was to be analysed using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference. This analysis was later removed from the protocol.

Change from baseline in the HJHS were to be compared using a mixed-effects model with repeated measures (MMRM) analysis. This analysis was later changed to be based on the Wilcoxon signed rank test.

Change from baseline in Haem-A-QoL/Haemo-QoL, HAL/pedHAL, and EQ-5D-5L was to be compared using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference.

PGIC-H was to be compared using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference.

Planned subgroup analyses

There were no subgroup analyses prespecified in the protocol or the SAP.

Error probabilities, adjustment for multiplicity and interim analyses

Type I error rate for the primary analysis of the primary endpoints were separately controlled for the inhibitor cohort, the non-inhibitor cohort for the EU and for the non-inhibitor cohort for regions outside of the EU.

Within the inhibitor cohort with prior on-demand therapy, the familywise Type I error rate was controlled at the 1-sided 0.025 level based on an hierarchical testing scheme including the following endpoints treated bleeds (primary), incidence of spontaneous bleeds, incidence of joint bleeds, incidence of target joint bleeds, incidence of total bleeds, physical function domain in Haem-A-QoL, total score in Haem-A-QoL at 6 months, EQ-5D-5L Index score at 6 months and EQ-VAS score at 6 months.

An interim analysis for futility had been planned but was later removed from the protocol and SAP.

Changes from protocol-specified analyses

The statistical analysis plan was amended five times. The sixth, most current version dates from the 31 January 2023. Versions 3 to 6 were finalized after the study initiation date of 09 March 2020. The data cutoff date was 29 April 2025 for the inhibitor cohort and 17 April 2023 for the non-inhibitor cohort.

A brief summary of the most important changes of versions 3 to 6, which were finalized after study initiation, is provided below:

Version 3 (15 April 2021): modification of definition of analysis sets, modification of estimand for primary endpoint, inclusion of justification for sample size calculation, modification of handling of missing data

Version 4 (17 May 2022): removal of interim futility analysis, removal of percentage of patients with no bleeding episodes from efficacy endpoints

Version 5 (26 July 2022): modifications of approach for Haem-A-QoL total score, EQ-VAS and EQ-5D-5L index score (addition to testing hierarchy, update of missing data handling)

Version 6 (31 January 2023): revision of missing data handling for HJHS and PROs, revision of definition of new untreated bleeds

Data quality assurance

Study monitoring

The sponsor - either directly or through delegated CROs - monitored the study through routine center visits and a Visit Log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to participant medical and laboratory records was permitted to verify entries on the study-specific CRFs. Telephone and e-mail contact was maintained with the investigators between center visits. In addition, the overall study conduct was subject to internal quality review by the sponsor.

The sponsor performed on-site and remote oversight to assess monitoring effectiveness and ensure compliance with the study protocol by investigational sites according to ICH/GCP, applicable standard operating procedures, and local regulation.

Investigator Meetings and Staff Training

Investigator staff training was provided by the sponsor and CRO during investigator meetings, initiation, and routine monitoring visits. The sponsor organized investigator and clinical research associate meetings before study start and during the study to provide information on the study intervention, the study rationale and design, responsibilities under ICH/FDA/GCP, and training on the detailed study requirements.

Laboratory Procedures

A central laboratory, Labcorp Central Laboratory Services, LP, was used to analyse the protocol-specified samples. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors. Established guidelines regarding age-appropriate maximum blood volume collection for adolescents and adults were followed, as described in the protocol.

Investigator Responsibilities

The investigators were responsible for all data entered in the CRFs and documented their review and approval of the data, verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents. The investigators and any qualified designees were responsible for detecting, documenting, and recording events that met the definition of an AE or SAE and remained responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event met the criteria for classification as an SAE or caused the participant to discontinue the study intervention/study.

Clinical Data Management

CRF data were captured via data entry by study center personnel or the CRO in a sponsor database system or a database system owned by a CRO. Participants also entered data directly into an electronic handheld diary, completed health outcome-related questionnaires using an electronic tablet device, and that data was subsequently transferred to the sponsor database system. Data quality checks were applied using manual and/or electronic verification methods. An audit trail was maintained to support data query resolution and any modification to the data.

Data to be recorded on the eDiary, on a handheld provisioned device by the participant or caregiver, included weekly injections of marstacimab and, when occurring, haemophilic bleeding episodes, including any exogenous factor replacement or bypass therapy that was required to treat the bleeds. The eDiary was programmed to provide reminders for the weekly injections of marstacimab and also to contact the investigator if an injection site reaction.

Note: in the event the eDiary was not available, a paper diary was to be used during the study.

Clinical Quality Assurance Audits

Audits of this study were included as part of the independent sponsor quality assessment performed by the sponsor.

This CSR has been subject to QC review by the sponsor or the sponsor's designee. The QC processes were reviewed by the sponsor's own independent quality assurance group.

Quality Tolerance Limits

A QTL was used for participants who had early study termination. The expected value for early study termination was 25 participants and the QTL was set at 36 participants. The limit was selected based on historical haemophilia study dropout rates. The team performed a monthly review of early terminated participants; identified root cause(s) of early termination to determine next steps; initiated site and CRA engagement to determine root cause(s) and implement CAPA(s); began proactive enrolment of additional participants to ensure adequate cohort sample size; CRA and SRP/SEP training.

Results

Participant flow

Participant flow and numbers analysed

Table 13: Disposition summary for inhibitor cohort (protocol B7841005_IN_CSR)

Number (%) of Participants	Inhibitor with On-Demand at OP n (%)	Inhibitor with Prophylaxis at OP n (%)	Overall n (%)
Disposition phase: Screening			
Participants Entered:			107
Discontinued*			47
Reason for discontinuation			
Adverse Event			1 (0.9)
Death			0
Lost to Follow-Up			0
Protocol Deviation			0
Screen Failure			44 (41.1)
Study Terminated By Sponsor			0
Withdrawal By Subject			1 (0.9)
Withdrawal By Parent/Guardian			1 (0.9)
Other			0
Completed			60 (56.1)
Disposition phase: Observational Phase (OP)			
Participants Entered:	57 (100.0)	3 (100.0)	60 (100.0)
Discontinued	7 (12.3)	0	7 (11.7)
Reason for discontinuation			
Adverse Event	1 (1.8)	0	1 (1.7)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	0	0	0
Physician Decision	0	0	0
Protocol Deviation	4 (7.0)	0	4 (6.7)
Study Terminated By Sponsor	0	0	0
Withdrawal By Subject	2 (3.5)	0	2 (3.3)
Medication Error Without Associated Adverse Event	0	0	0
No Longer Meets Eligibility Criteria	0	0	0
Withdrawal By Parent/Guardian	0	0	0
Failure to Meet Randomization Criteria	0	0	0
Global Deterioration Of Health Status	0	0	0
Other	0	0	0
Completed	50 (87.7)	3 (100.0)	53 (88.3)
Completed but not Entered ATP	2 (3.5)	0	2 (3.3)
Disposition phase: Active Treatment Phase (ATP)			
Participants Entered:	48 (100.0)	3 (100.0)	51 (100.0)
Discontinued	3 (6.3)	0	3 (5.9)
Reason for discontinuation			
Adverse Event	1 (2.1)	0	1 (2.0)
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	1 (2.1)	0	1 (2.0)
Physician Decision	0	0	0
Protocol Deviation	1 (2.1)	0	1 (2.0)
Study Terminated By Sponsor	0	0	0
Withdrawal By Subject	0	0	0
Medication Error Without Associated Adverse Event	0	0	0
No Longer Meets Eligibility Criteria	0	0	0
Withdrawal By Parent/Guardian	0	0	0
Failure to Meet Randomization Criteria	0	0	0
Global Deterioration Of Health Status	0	0	0
Other	0	0	0

Completed	45 (93.8)	3 (100.0)	48 (94.1)
Ongoing	0	0	0
Plan to Participate in the Extension Study B7841007	44 (91.7)	3 (100.0)	47 (92.2)
Disposition phase: Follow-Up			
Participants Entered:	2 (100.0)	0	2 (100.0)
Discontinued	0	0	0
Reason for discontinuation			
Adverse Event	0	0	0
Death	0	0	0
Lack of Efficacy	0	0	0
Lost to Follow-Up	0	0	0
Physician Decision	0	0	0
Protocol Deviation	0	0	0
Study Terminated By Sponsor	0	0	0
Withdrawal By Subject	0	0	0
Medication Error Without Associated Adverse Event	0	0	0
No Longer Meets Eligibility Criteria	0	0	0
Withdrawal By Parent/Guardian	0	0	0
Failure to Meet Randomization Criteria	0	0	0
Global Deterioration Of Health Status	0	0	0
Other	0	0	0
Completed	2 (100.0)	0	2 (100.0)

* Includes inhibitor participants who are in screening, discontinued at screening or completed screening but did not enter the OP as cohort assignment occurred upon entering the OP.
For inhibitor cohort with prior prophylaxis at OP, those who received at least one prophylactic or on-demand treatment in OP; for inhibitor cohort with on-demand at OP, those who completed any of the procedures for Visit 2 (OP baseline).
Percentage is calculated based on the number of participants entered at each phase.
Participants who discontinued or did not roll over to Study B7841007 were to complete the follow up phase.
Two participants shown as OP completed and ATP not entered: these participants entered but discontinued ATP before marstacimab dosing due to not meeting eligibility to enter the ATP.
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(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:
./nda1 cdisc/B7841005 IN CSR/adds s0011
Table 14.1.1.2.1i Marstacimab is for Pfizer internal use.

Recruitment

This study was conducted at 64 sites in 20 countries for participants with or without inhibitors: Bulgaria (2 sites), Canada (3 sites), China (5 sites), Croatia (2 sites), France (1 site), Hong Kong (2 sites), India (3 sites), Italy (3 sites), Japan (4 sites), Republic of Korea (3 sites), Mexico (2 sites), Oman (2 sites), Russian Federation (1 site), Saudi Arabia (2 sites), Serbia (5 sites), South Africa (1 site), Spain (5 sites), Taiwan (2 sites), Turkey (12 sites), and the US (4 sites). Please see table 13 for the inhibitor cohort.

Conduct of the study

Changes in the planned conduct of the study

The study protocol was amended a total of 7 times. Notably, 5 of the amendments were introduced after the study initiation date (FPFV) of 09 March 2020.

Data Cutoff Date (LPLV for Inhibitor cohort): 29 April 2025

Table 14: Protocol amendment summary of change table

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 7	24 March 2022
Protocol Amendment 6	13 July 2021
Protocol Amendment 5	20 November 2020
Protocol Amendment 4	08 June 2020
Protocol Amendment 3	12 March 2020
Protocol Amendment 2	12 November 2019
Protocol Amendment 1	25 April 2019
Original Protocol	11 December 2018

A brief summary of the most important protocol amendment changes is provided below:

Amendment 1 and **Amendment 2** included changes to the protocol before study initiation (09 March 2020).

Amendment 3: Included participation of prior prophylaxis participants in the US and Canada following a read-out of safety data provided from the Phase 2 program.

Amendment 4: For dose modification requirements a minimum body weight of 50 kg was added to allow dose escalation to 300 mg QW. New appendix added to the protocol detailing alternative study procedures to be followed during the COVID-19 global pandemic.

Amendment 5: Added the option to conduct safety assessments at a non-study centre when necessary to allow more flexibility in the event that an in-clinic visit could not be completed due to the COVID-19 global pandemic.

Amendment 6: Due to recruitment challenges and feedback received from clinical study sites, inclusion criteria were updated to enable recruitment of participants with moderately severe haemophilia B based on baseline factor activity level (factor activity level ≤2%) and haemorrhagic phenotype (≥4 bleeding episodes in the 6 months prior to study entry).

Allowed additional participants (approximately 20%) in order to provide sufficient enrolment into regions which had experienced delays created by the COVID-19 global pandemic.

Based on eDMC recommendation, revised to add that treatment with study intervention was to be suspended if a participant developed a presumed or confirmed symptomatic COVID-19 infection due to the potential for thrombotic events.

Amendment 7: removal of the interim analysis for futility within each participant population of interest planned after 50% of participants within each population of interest have completed the study as the interim analysis data cut time would be very close to the non-inhibitor cohort completions Endpoint "total coagulation factor or bypass product consumption" moved from secondary endpoints to tertiary/exploratory endpoints and removal of "percentage of participants with no treated bleeding episodes" from secondary endpoints, which will however be presented as part of descriptive analysis for the primary endpoint

Additional minor changes to the study protocol were introduced and were presented by the MAH in a total of 6 protocol administrative change letters.

Important protocol deviations

38 (63.3%) participants among the participants entering the OP had important protocol deviations reported, including those related to procedures/tests (20 participants), investigational product (10

participants), informed consent (7 participants), inclusion/exclusion criteria (5 participants), safety reporting (5 participants), concomitant medications (3 participants), and laboratory (2 participants). Participants with dosing/administration error protocol deviations reported a variety of different deviations that occurred typically one time and had no impact on overall efficacy or safety. One participant who did not adhere to the protocol-specified washout period prior to Visit 7 (1st dose of marstacimab) had no bleeds in the 4 weeks following Visit 7. The potential impact of this is addressed in the analysis to assess the impact of carryover effect from the OP. There were no observed efficacy or safety effects for participants with concomitant medication or dosing/administration error protocol deviations.

During the OP, 5 participants did not meet inclusion criteria for the inhibitor cohort per protocol and 1 participant met exclusion criteria for a known haemostatic defect other than haemophilia A or B. None of these participants entered the ATP.

17 (28.3%) participants had PRO questionnaires not completed at 1 or more visits that resulted in missing PRO data.

Laboratory measures (Factor VIII or IX activity, Factor VIII or IX inhibitor concentration values, and PF 1+2 concentration values) analysed at MD Biotec Corp (MDx, Bejing China) for 19 participants with inhibitors were considered to be unreliable at all timepoints due to lack of expected documentation and deviation from procedures at MDx. Affected Factor VIII or IX activity, and Factor VIII or IX inhibitor concentration values from MDx at screening and during active treatment for 19 participants with inhibitors from China were excluded from data output tables due to the MDx issue. Instead, factor activity and factor inhibitor concentration levels were obtained from historical and/or local laboratory sources (specimens taken prior to enrolment) and these values supported that the participants met enrolment criteria for severe haemophilia A and severe or moderately severe haemophilia B and that the participants were assigned to the appropriate cohort (inhibitor) for the study. Per protocol, local and historical values may be used to assess eligibility and selection in the study.

Affected PF 1+2 concentration values from MDx (visit level data) for a total of 18 (out of 19; 1 participant did not have any PF 1+2 data analysed at MDx) participants from China were excluded from data output tables, figures and listings. Differences were assessed in PF 1+2 summary outputs with and without inclusion of MDx data.

Table 15: Summary of important protocol deviations – inhibitor enrolled set (Protocol B7841005_IN_CSR)

Protocol Deviation Category/Subcategory	Inhibitor with On-Demand at OP (N=57) n (%)	Inhibitor with Prophylaxis at OP (N=3) n (%)	Overall (N=60) n (%)
With any protocol deviation	38 (66.7)	0	38 (63.3)
Concomitant Medications	3 (5.3)	0	3 (5.0)
Hemophilia product change occurred during study without consultation and agreement with Sponsor Medical Monitor, prior to implementation	2 (3.5)	0	2 (3.3)
Subject did not adhere to protocol-specified washout period prior to V7	1 (1.8)	0	1 (1.7)
Took prohibited concomitant medication/vaccine	1 (1.8)	0	1 (1.7)
Inclusion/Exclusion	5 (8.8)	0	5 (8.3)
Subject didn't meet inclusion for Inhibitor Cohort per protocol	5 (8.8)	0	5 (8.3)
Subject met exclusion criteria for known hemostatic defect other than Hemophilia A or B	1 (1.8)	0	1 (1.7)
Informed Consent	7 (12.3)	0	7 (11.7)
ICD not signed by impartial witness, when applicable	1 (1.8)	0	1 (1.7)
ICD signed by unauthorized site personnel	1 (1.8)	0	1 (1.7)
Revised ICD not signed at the first subject visits after the revised/approved ICD was available at site	4 (7.0)	0	4 (6.7)
Subject/LAR signed a superseded/outdated version of the ICD	1 (1.8)	0	1 (1.7)
Investigational Product	10 (17.5)	0	10 (16.7)
Dosing/Administration error	10 (17.5)	0	10 (16.7)
Subject met dose escalation criteria and increased dose decision implemented by Investigator without consultation with sponsor medical monitor.	1 (1.8)	0	1 (1.7)
Laboratory	2 (3.5)	0	2 (3.3)
Immunogenicity samples not collected	2 (3.5)	0	2 (3.3)
Procedures/Tests	20 (35.1)	0	20 (33.3)
Completed incorect PRO questionnaire(s) for subject age group	1 (1.8)	0	1 (1.7)
PROs questionnaires not completed	17 (29.8)	0	17 (28.3)
Subject did not complete the eDiary as instructed.	4 (7.0)	0	4 (6.7)
Safety Reporting	5 (8.8)	0	5 (8.3)
SAE/EIU not reported to Sponsor within specified timeframe	4 (7.0)	0	4 (6.7)
Study drug not temporarily interrupted in subject with symptomatic COVID-19	1 (1.8)	0	1 (1.7)

A participant with multiple deviations is counted once each in the corresponding categories and subcategories.
V7 stands for Visit 7 (Pre dose).
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Table 14.1.1.3i Marstacimab is for Pfizer internal use.

Baseline data

Study B7841005 was an adult (≥18 to <75 years of age) and adolescent (≥12 to <18 years of age) study conducted in male participants with severe haemophilia A or moderately severe to severe haemophilia B. The severity of haemophilia was confirmed either by documented historical evidence from a clinical laboratory prior to screening or by factor activity obtained from a clinical laboratory prior to study enrolment. Of note, even when baseline factor levels suggest moderate haemophilia, the presence of high titer inhibitors (>5 BU), lead to a clinical phenotype resembling severe haemophilia, due to difficulty in controlling bleeding in patients with inhibitors. The neutralizing impact of inhibitors effectively reduces factor activity levels in mild or moderate haemophilia to the severe range, resulting in a functional classification of severe haemophilia regarding bleeding risk and clinical management.

Enrolled participants in Study B7841005 (N=60) were primarily Asian (32, 53.3%) and White (19, 31.7%), with 8 (13.3%) Black/African American participants and 1 participant's race not reported. 51.7% and 20.0% of participants were from Asia and Europe, respectively.

Overall, across participants with inhibitors in Study B7841005:

- 47 (78.3%) participants had haemophilia A and 13 (21.7%) participants had haemophilia B.
- 44 (73.3%) participants were adults (≥18 to <75 years of age) and 16 (26.7%) participants were adolescents (≥12 to <18 years of age).
- The study population was characterized by a severe bleeding phenotype including a high prevalence of target joints at study entry. 42 out of 60 (70.0%) participants had one or more target joints at study entry and 13 out of 60 (21.7%) participants had 3 or more target joints at study entry.

All 60 participants were male with a median age of 23.0 years and individual values ranged from 12.0 to 75.0 years. The majority of participants (35, 58.3%) were in the 18-44 age range.

The median participant weight was 60.5 kg (range: 25.9 to 103.0 kg) and the median participant BMI was 21.6 kg/m2 (range: 12.7 to 38.3 kg/m2). Only 1 participant was less than the initial protocol-specified weight requirement of 30 kg (later amended to 35 kg) at screening; no protocol deviation was recorded. However, this participant had a weight kg at the time of marstacimab dosing, which met protocol criteria at the time.

The median participant height was 166.0 cm (range: 143.0 to 189.0 cm).

Most participants (55, 91.7%) had normal renal function (eGFR ≥90 mL/min/1.73 m2), while 4 (6.7%) participants had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m2).

Table 16: Demographic characteristics for inhibitor cohort with on-demand at OP by MITT status- inhibitor all safety set (protocol B7841005_IN_CSR)

	Inhibitor with On-Demand at OP (N=57)	
	MITT (N=48)	Not MITT (N=9)
Age (Years), n (%)		
< 18	12 (25.0)	3 (33.3)
18 - 44	29 (60.4)	4 (44.4)
45 - 64	6 (12.5)	1 (11.1)
65 - 74	0	1 (11.1)
≥ 75	1 (2.1)	0
n	48	9
Mean (SD)	28.2 (13.76)	29.9 (19.06)
Median	25.0	21.0
(Q1, Q3)	(17.0, 34.5)	(17.0, 33.0)
(Min, Max)	(12.0, 75.0)	(16.0, 67.0)
Sex, n (%)		
Male	48 (100.0)	9 (100.0)
Race, n (%)		
Black or African American	8 (16.7)	0
American Indian or Alaska Native	0	0
Asian	25 (52.1)	4 (44.4)
Native Hawaiian or Other Pacific Islander	0	0
White	15 (31.3)	4 (44.4)
Not Reported	0	1 (11.1)
Ethnicity, n (%)		
Hispanic or Latino	1 (2.1)	1 (11.1)
Not Hispanic or Latino	46 (95.8)	8 (88.9)
Not Reported	1 (2.1)	0
Baseline eGFR* (mL/min/1.73m²), n (%)		
≥ 90	43 (89.6)	9 (100.0)
≥ 60 to < 90	4 (8.3)	0
≥ 30 to < 60	0	0
<30	0	0
Missing	1 (2.1)	0
Weight (kg)		
n	48	9
Mean (SD)	60.6 (15.14)	71.6 (16.34)
Median	60.0	71.5
(Q1, Q3)	(52.3, 66.0)	(58.0, 78.8)
(Min, Max)	(25.9, 97.0)	(52.0, 103.0)
Height (cm)		
n	48	9
Mean (SD)	166.1 (9.12)	166.6 (7.80)
Median	166.0	168.0
(Q1, Q3)	(161.0, 173.0)	(164.0, 170.0)
(Min, Max)	(143.0, 189.0)	(153.0, 181.0)
Body Mass Index (kg/m²)		
n	48	9
Mean (SD)	21.7 (4.31)	25.8 (6.01)
Median	21.3	23.3
(Q1, Q3)	(18.9, 24.0)	(23.2, 29.4)
(Min, Max)	(12.7, 34.9)	(18.4, 38.3)

Table 17: Participant characteristics – inhibitor marstacimab safet set (protocol B7841105_IN_CSR)

	Inhibitor with On-Demand at OP (N=48)	Inhibitor with Prophylaxis at OP (N=3)	Overall (N=51)
Hemophilia Type, n (%)			
Hemophilia A	40 (83.3)	0	40 (78.4)
Hemophilia B	8 (16.7)	3 (100.0)	11 (21.6)
Age Groups, n (%)			
Adolescents (Ages 12 to < 18)	12 (25.0)	1 (33.3)	13 (25.5)
Adults (Ages 18 to < 75)	36 (75.0)	2 (66.7)	38 (74.5)
Age and Hemophilia Type, n (%)			
Adolescents Hem A	9 (18.8)	0	9 (17.6)
Adolescents Hem B	3 (6.3)	1 (33.3)	4 (7.8)
Adults Hem A	31 (64.6)	0	31 (60.8)
Adults Hem B	5 (10.4)	2 (66.7)	7 (13.7)
Factor VIII Inhibitor at Baseline, n (%)			
Participants with Hemophilia A	40 (100.0)	0	40 (100.0)
Positive	38 (95.0)	0	38 (95.0)
Negative*	2 (5.0)	0	2 (5.0)
Factor IX Inhibitor at Baseline, n (%)			
Participants with Hemophilia B	8 (100.0)	3 (100.0)	11 (100.0)
Positive	4 (50.0)	1 (33.3)	5 (45.5)
Negative*	4 (50.0)	2 (66.7)	6 (54.5)
ISTH Disease Severity, n (%)			
Mild	0	0	0
Moderate	0	0	0
Severe	48 (100.0)	3 (100.0)	51 (100.0)
Number of Target Joints at Baseline, n (%)			
0	13 (27.1)	1 (33.3)	14 (27.5)
1	13 (27.1)	0	13 (25.5)
2	10 (20.8)	1 (33.3)	11 (21.6)
≥ 3	12 (25.0)	1 (33.3)	13 (25.5)
Geographical Region, n (%)			
Asia	24 (50.0)	3 (100.0)	27 (52.9)
Europe	8 (16.7)	0	8 (15.7)
Middle East	5 (10.4)	0	5 (9.8)
North America	4 (8.3)	0	4 (7.8)
Southern Africa	7 (14.6)	0	7 (13.7)

Inhibitor Marstacimab safety set is defined as those who took at least 1 dose of marstacimab.
* Participants who have a previously documented inhibitor titer ≥5 BU/mL while on factor-replacement therapy prior to study enrolment, but who do not meet the quantitative inhibitor criteria at the time of Screening and whose condition precludes re-challenge with FVIII or FIX replacement) were considered eligible after discussion and agreement with Pfizer medical monitor.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:28) Source Data: adsl Table Generation: 30JUL2025 (06:34)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adsl_s001_si

Medical History and Concurrent Illnesses

The most common conditions in study participants (≥5%) were haemophilic arthropathy (15, 25.0%), hepatitis (7 [11.7%] with hepatitis C, 6 [10.0%] with hepatitis B, and 1 [1.7%] each with chronic hepatitis B and chronic hepatitis C, respectively), hypertension (8, 13.3%), arthropathy (7, 11.7%: all of whom also reported haemophilic arthropathy), circumcision (7, 11.7%), haemorrhoids (5, 8.3%), nephrolithiasis (4, 6.7%), synoviorthesis (4, 6.7%), and gastroesophageal reflux disease and headache (3, 5.0% each).

Outcomes and estimation

Primary Efficacy Endpoint: ABR of Treated Bleeds (On-Demand at OP)

Marstacimab prophylaxis demonstrated superiority (2-sided p-value <0.0001) over on-demand treatment as measured by ABR of treated bleeds.

The ABR of treated bleeds was the primary efficacy endpoint in Study B7841005. Of the 48 participants who completed the 6-month OP and received at least 1 dose of marstacimab in the ATP, the mean estimated ABR was 1.39 (95% CI: 0.85, 2.29) for marstacimab prophylaxis during the ATP compared to the mean estimated ABR of 19.78 (95% CI: 16.12, 24.27) for on-demand treatment during the OP, with the resulting estimated ABR ratio of 0.070 (95% CI: 0.042, 0.118). The reduction in ABR of treated bleeds from the OP was 93%. With the upper bound of the 95% CI for the ABR ratio less than 0.5, these results achieved the predetermined criterion for establishing the superiority (2-sided p-value <0.0001) of marstacimab over on-demand treatment. Of the 48 participants who completed the 6-month OP, 1 (2.1%) participant did not have any treated bleeds; of the 45 participants who completed the 12-month ATP, 26 (54.2%) participants did not have any treated bleeds.

The primary efficacy analysis/endpoint evaluated the efficacy of marstacimab at a 150 mg dose via censoring bleeding records on or after a dose increase to 300 mg. The duration that participants were on an escalated dose was not included in the primary endpoint assessment.

ABR for treated bleeds for the inhibitor cohort with on-demand treatment at OP is summarized in Table 18 below.

Table 18: Primary analysis of ABR for treated bleeds for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

ABR[1]	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Descriptive Summary		
Mean	19.81	1.46
SD	14.386	2.702
Median	16.42	0.00
Q1, Q3	9.98, 26.47	0.00, 2.03
Min, Max	0.00, 69.10	0.00, 14.91
Categorical Summary		
Completed the Phase	48 (100.0)	45 (93.8)
0 bleed	1 (2.1)	26 (54.2)
1 bleed	4 (8.3)	5 (10.4)
2 bleeds	1 (2.1)	5 (10.4)
≥ 3 bleeds	42 (87.5)	9 (18.8)
Discontinued the Phase	0 (0.0)	3 (6.3)
0 bleed	0 (0.0)	2 (4.2)
1 bleed	0 (0.0)	1 (2.1)
2 bleeds	0 (0.0)	0 (0.0)
≥ 3 bleeds	0 (0.0)	0 (0.0)
Model-based Summary[2]		
Mean Estimate	19.78	1.39
95% CI	(16.12, 24.27)	(0.85, 2.29)
Treatment Comparison based on the Marstacimab/On-demand ratio[2]		
Ratio Estimate		0.070
95% CI[3]		(0.042, 0.118)
p-value[4]		<.0001

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with log link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylactic or on-demand) as a factor, and log time on treatment as an offset variable to account for different duration on treatment.
3. Superiority of marstacimab prophylaxis is declared when the 95% CI lies below 0.5.
4. P-value for the null hypothesis (ratio = 0.5).
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (07:54)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:
./nda1 cdisc/B7841005 IN CSR/adhe s1001
Table 14.2.1.1.1i Marstacimab is for Pfizer internal use.

Intercurrent events

Dose modification

4 out of 51 (7.84%) participants (3 with haemophilia A and 1 with haemophilia B, with prior on-demand treatment) had their marstacimab dose increased from 150 mg to 300 mg SC weekly, with their 300 mg SC dose escalation initiated between Study Day 179-246.

For the 4 participants who had their marstacimab dose increased from 150 mg to 300 mg, the median durations for 150 mg and 300 mg treatment were 240.0 and 134.0 days, respectively, with corresponding mean ABRs of 5.89 (before dose increase) and 3.71 (on or after dose increase).

Bypass product consumption

For the prior on-demand group, the mean total (per year) of total bypass product consumption was:

- 1443.58 (SD: 1797.278) IU/kg during the OP and 106.80 (SD: 66.767) IU/kg during the ATP for aPCC
- 6062.59 (SD: 10,184.921) µg/kg during the OP and 1064.69 (SD: 1878.207) µg/kg during the ATP for rFVIIa

Total days requiring bypass product treatment were also reduced during the ATP (mean exposure: 3 days, median exposure: 0 days per participant) when compared to the OP (mean exposure: 21 days, median exposure: 14 days per participant).

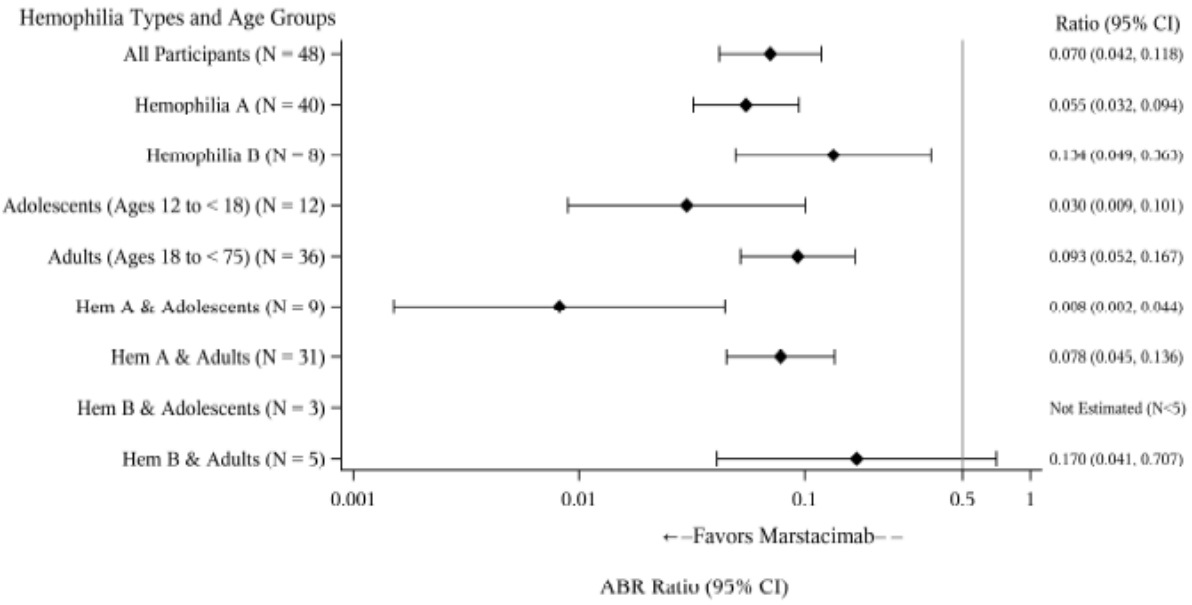
Subgroup Analysis: ABR of Treated Bleeds (On-Demand at OP)

A comparison of the ABRs of treated bleeds for participants with inhibitors and prior on-demand treatment is summarized by haemophilia types and age groups in Figure 22, and ethnicity groups and geographic regions in Figure 23 below.

The descriptive mean ABR of treated bleeds for participants with haemophilia A was 1.08 for marstacimab prophylaxis during the ATP compared to the mean ABR of 18.99 for on-demand treatment during the OP.

The descriptive mean ABR of treated bleeds for participants with haemophilia B was 3.40 for marstacimab prophylaxis during the ATP compared to the mean ABR of 23.89 for on- demand treatment during the OP. One adult participant with haemophilia B had an ABR value of 14.91 during the ATP, which had a large impact on the mean ABRs for the haemophilia B and haemophilia B adult subgroups considering the small sample sizes (N=8 and N=5, respectively). When this participant was excluded from the analysis, the mean ABRs for the haemophilia B and haemophilia B adult subgroups decreased to 1.76 (range: 0, 6.87) and 1.11 (range: 0, 3.05), respectively. This adult haemophilia B participant had an ABR of 16.60 during the OP and an ABR of 14.91 while on 150 mg marstacimab during the ATP; the participant was dose escalated on Study Day 246 and following dose escalation, their ABR decreased to 2.73.

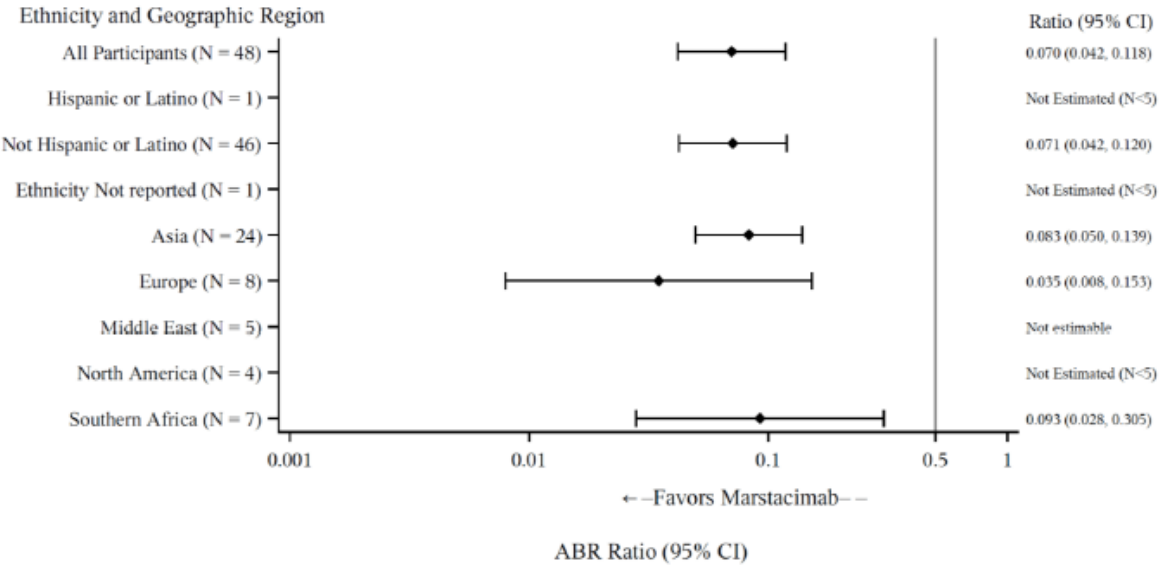
Figure 22: Comparison of ABRs for treated bleeds for haemophilia types and age groups for inhibitor cohort with on-demand at OP -MITT set



Reference: Figure 14.2.1.1.8i

PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 22AUG2025 (13:55)(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhe_f1005

Figure 23: Comparison of ABRs for treated bleeds for ethnicity groups and geographic regions for inhibitir cohort with on-demand at OP-MITT set



PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (13:44) (Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: . /nda1_cdisc/B7841005_IN_CSR/adhe_f1007

Source: Figure 14.2.1.1.10i.

A subset descriptive summary of the ABR for treated bleeds by haemophilia type and age group for the inhibitor cohort with on-demand treatment at OP is provided in below Table.

Table 19: Subset descriptive summary of ABR for treated bleeds by haemophilia type and age group for inhibitor cohort with on demand at OP-MITT set (protocol B7841005_IN_CSR)

Subset	ABR[1] Descriptive Summary	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Hemophilia A	N	40	40
	Mean	18.99	1.08
	SD	14.960	1.738
	Median	16.05	0.00
	Q1, Q3	8.98, 23.44	0.00, 2.01
	Min, Max	0.00, 69.10	0.00, 6.07
Hemophilia B	N	8	8
	Mean	23.89	3.40
	SD	10.943	5.198
	Median	21.07	1.19
	Q1, Q3	16.33, 31.93	0.00, 4.96
	Min, Max	9.93, 42.52	0.00, 14.91
Adolescents: Ages 12-17	N	12	12
	Mean	27.66	0.82
	SD	11.202	2.002
	Median	26.47	0.00
	Q1, Q3	17.30, 36.99	0.00, 0.50
	Min, Max	12.97, 45.19	0.00, 6.87
Adults: Ages 18-74	N	36	36
	Mean	17.19	1.68
	SD	14.499	2.890
	Median	15.76	0.00
	Q1, Q3	7.92, 21.14	0.00, 2.54
	Min, Max	0.00, 69.10	0.00, 14.91
Hem A, Adolescents	N	9	9
	Mean	27.48	0.22
	SD	11.423	0.665
	Median	28.10	0.00
	Q1, Q3	17.30, 36.32	0.00, 0.00
	Min, Max	12.97, 45.19	0.00, 2.00
Hem B, Adolescents	N	3	3
	Mean	28.22	2.62
	SD	12.946	3.713
	Median	24.85	1.00
	Q1, Q3	17.29, 42.52	0.00, 6.87
	Min, Max	17.29, 42.52	0.00, 6.87
Hem A, Adults	N	31	31
	Mean	16.52	1.32
	SD	15.108	1.878
	Median	13.97	0.00
	Q1, Q3	7.77, 19.57	0.00, 2.03
Hem A, Adults	Min, Max	0.00, 69.10	0.00, 6.07
Hem B, Adults	N	5	5
	Mean	21.29	3.87
	SD	10.163	6.299
	Median	16.60	1.37
	Q1, Q3	16.05, 29.94	0.00, 3.05
	Min, Max	9.93, 33.93	0.00, 14.91

1. ABR= annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:35)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhe_s1005

Supplementary/Sensitivity Analysis: ABR of Treated Bleeds (On-Demand at OP)

Supplementary/sensitivity analyses of the ABR of treated bleeds for participants with inhibitors and prior on-demand treatment at OP are summarized in Table 20 below.

The ABR of treated bleeds for the first and second half of ATP is descriptively summarised in the table below for completed participants who remained on a dose of 150 mg marstacimab SC QW during the full ATP with inhibitors and prior on-demand treatment at OP. The mean ABR of participants remaining on the 150 mg marstacimab SC QW dose was lower in the second 6 months of ATP compared with that in the first 6 months (0.79 vs 1.41, respectively).

Table 20: Supplementary /sensitivity analysis of ABR for treated bleeds for inhibitor cohort with on-demand at OP – MITT set (protocol B7841005_IN_CSR)

Supplementary Analysis Type	Estimated ABR[1] Ratio: Marstacimab/On-Demand	95% CI
Analysis to assess the impact of preventative infusion		
Including bleeding during preventative infusion	0.070	(0.042, 0.117)
Analyses to assess the impact of marstacimab dose increase		
Number of participants with dose increase: 4		
Including data after a dose increase	0.075	(0.046, 0.121)
Imputing the portion after a dose increase using the data before the dose increase	0.075	(0.043, 0.129)
Tipping point analysis[2]	Tipping Multiplier: 14	
	0.190	(0.069, 0.525)
Analyses to assess the impact of treatment discontinuation or potentially missing bleeding records		
Number of participants with ATP discontinuation or dosing gap (≥ 35 days) during which time no bleed was reported: 3		
Imputing the portion after treatment discontinuation using the data during treatment and during dosing gap using the data before and after the dosing gap	0.074	(0.046, 0.121)
Tipping point analysis[2]	Tipping Multiplier: 196	
	0.202	(0.081, 0.500)
Analysis to assess the impact of carryover effect from the observational phase		
Excluding the first month data after initiation of marstacimab	0.065	(0.037, 0.112)
Analysis to assess the seasonal effect on bleeding		
Include only the portion of ATP that match the calendar time of OP	0.048	(0.026, 0.087)

1. ABR= annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Using ABRs calculated combining bleeds before the event (dose increase or treatment discontinuation) and assuming the bleed rate after the event as multiples of successively larger (> 1) factors of the former.
Note: All analyses used the same model used in the primary efficacy analysis.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:19)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhe_s1002
Table 14.2.1.1.2i Marstacimab is for Pfizer internal use.

Table 21: Descriptive summary of ABR for treated bleeds for the 1st and 2nd half of ATP for completed participants for inhibitor cohort with on-demand at OP – MITT set (protocol B7841005_IN_CSR)

ABR[1] Descriptive Summary	First Half of ATP[2] (N=41)	Second Half of ATP[2] (N=41)
N Completers[3]	41	41
Mean	1.41	0.79
SD	2.687	1.626
Median	0.00	0.00
Q1, Q3	0.00, 2.00	0.00, 2.01
Min, Max	0.00, 9.98	0.00, 8.12

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. ATP = active treatment period, the 1st half includes Day 1 to 182 and the 2nd half includes Day 183 to the end of ATP.
3. Excludes participants with marstacimab dose increase and discontinued participants.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:19)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:
./nda1 cdisc/B7841005 IN CSR/adhe s1003
Table 14.2.1.1.5i Marstacimab is for Pfizer internal use.

Table 22: Descriptive summary of ABR for treated bleeds and treatment duration before and after the dose increase for participants with dose increase for inhibitor cohort – marstacimab safety set (protocol B781005_IN_CSR)

Descriptive Summary	Before Dose Increase (N=51)	On or After the Dose Increase (N=51)
Treatment Duration (days)		
N with Dose Increase	4	3
Mean	225.8	130.0
SD	31.93	8.72
Median	240.0	134.0
Q1, Q3	208.5, 243.0	120.0, 136.0
Min, Max	178.0, 245.0	120.0, 136.0
ABR[1]		
N with Dose Increase	4	3
Mean	5.89	3.71
SD	6.351	1.444
Median	4.33	3.04
Q1, Q3	2.05, 9.73	2.73, 5.37
Min, Max	0.00, 14.91	2.73, 5.37

1. ABR= annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days. One participant received two 300mg doses after dose escalation. He subsequently returned to 150mg and completed the study. This participant was not summarized in after dose escalation column.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 20AUG2025 (08:58)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhe_s1003a
Table 14.2.1.1.5.1i Marstacimab is for Pfizer internal use.

Inhibitor Cohort With Routine Prophylaxis at OP

For the prior prophylaxis group (N=3), the mean and median incidence of treated bleeds were 1.03 (SD: 1.020) and 1.03, respectively, for marstacimab prophylaxis during the ATP compared to the mean and median incidence of treated bleeds of 7.61 (SD: 2.948) and 8.30, respectively, for prior prophylactic treatment during the OP.

Secondary Efficacy Endpoints (On-Demand at OP)

Similar to the intercurrent event handling for the primary endpoint, data collected after dose escalation are not included in the analysis of any secondary endpoints related to bleeds, to avoid over-estimation of the effect of the intended dose.

Incidence of Joint Bleeds (On-Demand at OP)

In study B7841005 the ABR ratio for joint bleeds was estimated to be 0.072 (95% CI: 0.038, 0.138, marstacimab vs on-demand), see Table 23.

Table 23: Analysis of incidence of joint bleeds for inhibitor cohort with on-demand at OP – MITT set (protocol B7841005_IN_CSR)

ABR[1]	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Descriptive Summary		
Mean	15.17	1.15
SD	13.172	2.650
Median	11.66	0.00
Q1, Q3	7.17, 17.68	0.00, 1.01
Min, Max	0.00, 57.26	0.00, 14.91
Categorical Summary		
Completed the Phase	48 (100.0)	45 (93.8)
0 bleed	4 (8.3)	31 (64.6)
1 bleed	3 (6.3)	5 (10.4)
2 bleeds	2 (4.2)	2 (4.2)
≥ 3 bleeds	39 (81.3)	7 (14.6)
Discontinued the Phase	0 (0.0)	3 (6.3)
Model-based Summary[2]		
Mean Estimate	15.15	1.10
95% CI	(11.87,19.34)	(0.59, 2.04)
Treatment Comparison based on the Marstacimab/On-Demand Ratio[3]		
Ratio Estimate		0.072
95% CI[3]		(0.038, 0.138)
p-value[4]		<.0001

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with log link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylactic or on-demand) as a factor, and time on treatment as an offset variable to account for different duration on treatment.
3. Superiority of marstacimab prophylaxis is declared when the 95% CI lies below 0.5.
4. P-value for the null hypothesis (ratio 0.5).
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:31)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:

Incidence of Spontaneous Bleeds (On-Demand at OP)

In study B7841005 the ABR ratio for spontaneous bleeds was estimated to be 0.057 (95% CI: 0.035, 0.092, marstacimab vs on-demand treatment), see Table 24.

Table 24: Analysis of incidence of spontaneous bleeds for inhibitor cohort with on-demand at OP- MITTset (protocol B7841005_IN-CSR)

ABR[1]	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Descriptive Summary		
Mean	15.30	0.89
SD	12.742	1.525
Median	11.49	0.00
Q1, Q3	7.75, 21.67	0.00, 1.68
Min, Max	0.00, 53.89	0.00, 6.87
Categorical Summary		
Completed the Phase	48 (100.0)	45 (93.8)
0 bleed	5 (10.4)	28 (58.3)
1 bleed	4 (8.3)	6 (12.5)
2 bleeds	1 (2.1)	8 (16.7)
≥ 3 bleeds	38 (79.2)	3 (6.3)
Discontinued the Phase	0 (0.0)	3 (6.3)
Model-based Summary[2]		
Mean Estimate	15.27	0.87
95% CI	(12.07,19.31)	(0.53, 1.43)
Treatment Comparison based on the Marstacimab/On-Demand Ratio[3]		
Ratio Estimate		0.057
95% CI[3]		(0.035, 0.092)
p-value[4]		<.0001

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with log link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylactic or on-demand) as a factor, and time on treatment as an offset variable to account for different duration on treatment.
3. Superiority of marstacimab prophylaxis is declared when the 95% CI lies below 0.5.
4. P-value for the null hypothesis (ratio 0.5).
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:47)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhe_s1007
Table 14.2.1.2.2i Marstacimab is for Pfizer internal use.

Incidence of Target Joint Bleeds (Treated) (On-Demand at OP)

In study B7841005 the ABR ratio for target joint bleeds was estimated to be 0.124 (95% CI: 0.061, 0.251, marstacimab vs on-demand treatment), see Table 25.

Table 25: Analysis of incidence of target joint bleeds for inhibitor cohort with on-demand at OP-MITT set (Protocol B7841005_IN_TJ_ERRATA)

ABR[1]	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Descriptive Summary		
Mean	6.34	0.82
SD	8.512	2.357
Median	2.09	0.00
Q1, Q3	0.00, 10.84	0.00, 0.00
Min, Max	0.00, 42.52	0.00, 13.42
Categorical Summary		
Completed the Phase	48 (100.0)	45 (93.8)
0 bleed	20 (41.7)	36 (75.0)
1 bleed	5 (10.4)	2 (4.2)
2 bleeds	3 (6.3)	2 (4.2)
≥ 3 bleeds	20 (41.7)	5 (10.4)
Discontinued the Phase	0 (0.0)	3 (6.3)
Model-based Summary[2]		
Mean Estimate	6.30	0.79
95% CI	(4.32, 9.20)	(0.36, 1.74)
Treatment Comparison based on the Marstacimab/On-Demand Ratio[3]		
Ratio Estimate		0.126
95% CI[3]		(0.062, 0.256)
p-value[4]		0.0001

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with log link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylactic or on-demand) as a factor, and time on treatment as an offset variable to account for different duration on treatment.
3. Superiority of marstacimab prophylaxis is declared when the 95% CI lies below 0.5.
4. P-value for the null hypothesis (ratio 0.5).
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (15:54) Source Data: adabr Table Generation: 27NOV2025 (10:38)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:

Incidence of Total Bleeds (Treated and Untreated) (On-Demand at OP)

In study B7841005 the ABR ratio for total bleeds was estimated to be 0.160 (95% CI: 0.102, 0.249, marstacimab vs on-demand treatment), see Table 26.

Table 26: Analysis of incidence of total bleeds (treated and untreated) for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

ABR[1]	On-Demand During OP (N=48)	Marstacimab Prophylaxis During ATP (N=48)
Descriptive Summary		
Mean	27.40	4.48
SD	18.621	8.056
Median	21.91	2.02
Q1, Q3	15.88, 37.28	0.00, 4.79
Min, Max	0.00, 83.83	0.00, 38.66
Categorical Summary		
Completed the Phase	48 (100.0)	45 (93.8)
0 bleed	1 (2.1)	15 (31.3)
1 bleed	2 (4.2)	5 (10.4)
2 bleeds	1 (2.1)	6 (12.5)
≥ 3 bleeds	44 (91.7)	19 (39.6)
Discontinued the Phase	0 (0.0)	3 (6.3)
Model-based Summary[2]		
Mean Estimate	27.29	4.36
95% CI	(22.54,33.03)	(2.65, 7.18)
Treatment Comparison based on the Marstacimab/On-Demand Ratio[3]		
Ratio Estimate		0.160
95% CI[3]		(0.102, 0.249)
p-value[4]		<.0001

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with log link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, treatment (marstacimab prophylaxis or on-demand) as a factor, and time on treatment as an offset variable to account for different duration on treatment.
3. Superiority of marstacimab prophylaxis is declared when the upper bound of the 95% CI is lies below 0.5.
4. P-value for the null hypothesis (ratio 0.5).
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: adabr Table Generation: 30JUL2025 (08:47)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:
./nda1 cdisc/B7841005 IN CSR/adhe s1009
Table 14.2.1.2.4i Marstacimab is for Pfizer internal use.

Haemophilia Joint Health Score (HJHS) (On-Demand at OP)

For the prior on-demand group, the estimated median change from baseline in the HJHS total score at 6 months was -3.9 (95% CI: -6.1, -1.7) for marstacimab prophylaxis during the ATP compared to -1.1 (95% CI: -4.0, 1.9) for on-demand treatment during the OP, with the resulting estimated median difference of -2.2 (95% CI: -5.7, 1.4), see Table 27.

Table 27: Non-parametric analysis of change from baseline in haemophilia joint health score (HJHS)* for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

HJHS Total Score		On-Demand During OP (N=48)[2]	Marstacimab Prophylaxis During ATP (N=48)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	-1.1	-3.9
	95% CI	(-4.0, 1.9)	(-6.1, -1.7)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-2.2
	95% CI		(-5.7, 1.4)
	p-value		0.2341
	Effect Size[3]		0.11
Change from Baseline at 12 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	-1.1	-3.7
	95% CI	(-4.0, 1.9)	(-6.3, -1.0)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-2.5
	95% CI		(-6.7, 1.6)
	p-value		0.2309

1. Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
2. Change from baseline at 6 months is presented both at 6 months and 12 months, as the treatment duration for OP was 6 months.
3. Effect Size (ES) is calculated as |estimated median difference|/ (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
* Total Score is reported; it ranges from 0 to 124 with higher score indicating worse joint health.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:58) Source Data: adhj Table Generation: 30JUL2025 (08:48)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:

Health-Related Quality-of-Life Outcomes (On-Demand at OP)

The reference treatment duration in the OP was 6 months, while marstacimab prophylaxis was administered for 12 months during the ATP, therefore, the main comparison timepoint between the OP and the ATP is at 6 months for each phase (OP Visit 5 and ATP Visit 14), and the ATP 12-month comparison utilizes 6-month visit results from the OP (OP Visit 5 and ATP Visit 20).

Haem-A-QoL (≥17 Years) and Haemo-QoL (Adolescents 12 to <17 Years) (On-Demand at OP)

For the Haem-A-QoL (participants ≥17 years) physical health domain, the estimated median change from baseline at 6 months was -20.8 (95% CI: -29.7 -11.9) for marstacimab prophylaxis during the ATP compared to 2.2 (95% CI: -6.6, 11.0) for on-demand treatment during the OP with a resulting estimated median difference of -25.9 (95% CI: -37.5, -14.2), see Table 28.

For the Haem-A-QoL (participants ≥17 years) total score, the estimated median change from baseline at 6 months was -12.0 (95% CI: -18.3, -5.7) for marstacimab prophylaxis during the ATP compared to 1.5 (95% CI: -2.4, 5.5) for on-demand treatment during the OP with a resulting estimated median difference of -13.5 (95% CI: -19.8, -7.2), see Table 29.

Table 28: Non-parametric analysis of change from baseline in total score and physical health domain in HAEM-A-QOL* for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

Total Score		On-Demand During OP (N=35)[2]	Marstacimab Prophylaxis During ATP (N=35)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	1.5	-12.0
	95% CI	(-2.4, 5.5)	(-18.3, -5.7)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-13.5
	95% CI		(-19.8, -7.2)
	p-value		<.0001
	Effect Size[3]		0.74
Change from Baseline at 12 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	1.5	-11.0
	95% CI	(-2.4, 5.5)	(-17.6, -4.3)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-13.6
	95% CI		(-22.0, -5.2)
	p-value		0.0016

* Assessed for participants 17 to < 75 years of age.
1. Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
2. Change from baseline at 6 months is presented both at 6 months and 12 months, as the treatment duration for OP was 6 months.
3. Effect Size (ES) is calculated as |estimated median difference|/ (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
Transformed Scale Score is reported, it ranges from 0 to 100 with higher score indicating worse quality of life.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2025 (13:22) Source Data: adhq Table Generation: 30JUL2025 (09:46)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File:

Table 29: Non-parametric analysis of change from baseline in total score and physical health domain in HAEM-A-QoL* for inhibitor cohort with on demand at OP-MITT set (protocol B7841005_IN-CSR)

Physical Health		On-Demand During OP (N=35)[2]	Marstacimab Prophylaxis During ATP (N=35)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	2.2	-20.8
	95% CI	(-6.6, 11.0)	(-29.7, -11.9)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-25.9
	95% CI		(-37.5, -14.2)
	p-value		<.0001
	Effect Size[3]		1.02
Change from Baseline at 12 Months of Treatment	Non-parametric Summary[1]		
	Median Estimate	2.2	-20.9
	95% CI	(-6.6, 11.0)	(-31.1, -10.8)
	Treatment Comparison[1]: Marstacimab - On-Demand		
	Estimated Median Difference		-24.6
	95% CI		(-35.0, -14.2)
	p-value		<.0001

* Assessed for participants 17 to < 75 years of age.
1. Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
2. Change from baseline at 6 months is presented both at 6 months and 12 months, as the treatment duration for OP was 6 months.
3. Effect Size (ES) is calculated as |estimated median difference|/ (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
Transformed Scale Score is reported, it ranges from 0 to 100 with higher score indicating worse quality of life.
PFIZER CONFIDENTIAL SDTM Creation: 28JUL2025 (13:22) Source Data: adhq Table Generation: 30JUL2025 (09:46)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/adhaq_s1002a
Table 14.2.1.3.2.1i Marstacimab is for Pfizer internal use.

EQ-5D-5L (On-Demand at OP)

For EQ-5D-5L index score, the estimated median change from baseline at 6 months was 0.1687 (95% CI: 0.0718, 0.2657) for marstacimab prophylaxis during the ATP compared to 0.0026 (95% CI: -0.0669, 0.0721) for on-demand treatment during the OP, with the resulting estimated median difference of 0.1043 (95% CI: 0.0060, 0.2027), see Table 30.

For EQ-VAS, the estimated median change from baseline at 6 months was 10.2 (95% CI: 4.2, 16.2) for marstacimab prophylaxis during the ATP compared to 1.5 (95% CI: -6.2, 9.3) for on-demand treatment during the OP, with the resulting estimated median difference of 7.5 (-1.9, 17.0), see Table 31.

Table 30: Non-parametric analysis of change from baseline in EQ-5D for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

EQ-5D-5L index[1]		On-Demand During OP (N=48)[4]	Marstacimab Prophylaxis During ATP (N=48)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary[2]		
	Median Estimate	0.0026	0.1687
	95% CI	(-0.0669, 0.0721)	(0.0718, 0.2657)
	Treatment Comparison[2]: Marstacimab - On-Demand		
	Estimated Median Difference		0.1043
	95% CI		(0.0060, 0.2027)
	p-value		.0377
	Effect Size[5]		0.37
Change from Baseline at 12 Months of Treatment	Non-parametric Summary[2]		
	Median Estimate	0.0026	0.1261
	95% CI	(-0.0669, 0.0721)	(0.0124, 0.2398)
	Treatment Comparison[2]: Marstacimab - On-Demand		
	Estimated Median Difference		0.0950
	95% CI		(-0.0139, 0.2039)
	p-value		.0874

1. Higher scores indicate better health states with the maximum value of 1 (EQ-5D-5L index score ranges from -0.594 to 1). UK look-up value was applied to all participants.
2. Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
3. Measures the participant's self-rated health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
4. Change from baseline at 6 months is presented both at 6 months and 12 months, as the treatment duration for OP was 6 months.
5. Effect Size (ES) is calculated as |estimated median difference|/ (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: ade5 Table Generation: 05AUG2025 (03:04)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/ade5_s001
Table 14.2.1.3.12.1i Marstacimab is for Pfizer internal use.

Table 31: Non-parametric analysis of change from baseline in EQ-5D for inhibitor cohort with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

EQ-VAS[3]		On-Demand During OP (N=48)[4]	Marstacimab Prophylaxis During ATP (N=48)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary[2]		
	Median Estimate	1.5	10.2
	95% CI	(-6.2, 9.3)	(4.2, 16.2)
	Treatment Comparison[2]: Marstacimab - On-Demand		
	Estimated Median Difference		7.5
	95% CI		(-1.9, 17.0)
	p-value		.1184
	Effect Size[5]		0.33
Change from Baseline at 12 Months of Treatment	Non-parametric Summary[2]		
	Median Estimate	1.5	13.3
	95% CI	(-6.2, 9.3)	(4.3, 22.2)
	Treatment Comparison[2]: Marstacimab - On-Demand		
	Estimated Median Difference		10.5
	95% CI		(0.0, 20.9)
	p-value		.0492

1. Higher scores indicate better health states with the maximum value of 1 (EQ-5D-5L index score ranges from -0.594 to 1). UK look-up value was applied to all participants.
2. Exact confidence interval using Walsh averages, p-value from Wilcoxon Signed Rank test. Missing values were imputed using multiple imputation methods based on MAR assumption.
3. Measures the participant's self-rated health state on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).
4. Change from baseline at 6 months is presented both at 6 months and 12 months, as the treatment duration for OP was 6 months.
5. Effect Size (ES) is calculated as |estimated median difference|/ (Standard Deviation [SD] at OP baseline); small ES = 0.2 SD units; medium ES = 0.5; large ES = 0.8.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (16:54) Source Data: ade5 Table Generation: 05AUG2025 (03:04)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B7841005_IN_CSR/ade5_s001
Table 14.2.1.3.12.1i Marstacimab is for Pfizer internal use.

PGIC-H (On-Demand at OP)

For PGIC-H, the estimated median difference at 6 months was -2.0 (95% CI: -2.5, -1.5; p- value <0.0001) for marstacimab prophylaxis during the ATP compared with on-demand treatment during the OP.

HAL2 (≥17 Years) and pedHAL (Adolescents 12 to <17 Years) (On-Demand at OP)

For the HAL2 (participants ≥17 years) total score, the estimated median change from baseline at 6 months was 10.6 (95% CI: 4.8, 16.4) for marstacimab prophylaxis during the ATP compared to 0.4 (95% CI: -5.2, 5.9) for on-demand treatment during the OP, with the resulting estimated median difference of 10.4 (95% CI: 2.7, 18.2; p-value = 0.0085).

For the pedHAL (adolescents 12 to <17 years) total score, the estimated median change from baseline at 6 months was 14.4 (95% CI: 1.1, 27.8) for marstacimab prophylaxis during the ATP compared to -

4.4 (95% CI: -20.9, 12.1) for on-demand treatment during the OP, with the resulting estimated median difference of 20.6 (95% CI: -2.2, 43.3; p-value = 0.0760).

Ancillary analyses

Sensitivity Analyses: ABR of Treated Bleeds (On-Demand at OP)

Table 32 compares the ABRs of treated bleeds during the OP versus the ATP by the number of target joints at the OP baseline. The table displays the following:

- 14 out of 48 participants had no target joints at the OP baseline. The remaining 34 out of 48 participants had one or more target joints at baseline, with 12 out of 48 participants having ≥3 target joints.
- On-demand cohort participants with target joints at the OP baseline tend to have higher ABRs during both the OP and the ATP.
- The ABR was consistently reduced with marstacimab in the ATP across target joint subgroups (by number of target joints at OP baseline).

Table 32: ABR at OP and ATP by number of target joints at OP baseline for inhibitor cohort with on-demand at OP-MITT set (protocol B78401005_IN_TJ_ERRATA)

Target Joint Grouping	ABR[1] Descriptive Summary	OP ABR (N=48)	ATP ABR (N=48)
0	N	14	14
	Mean	12.68	0.73
	SD	17.325	1.296
	Median	8.88	0.00
	Q1, Q3	2.12, 14.53	0.00, 1.01
	Min, Max	0.00, 69.10	0.00, 4.10
1	N	12	12
	Mean	26.34	2.00
	SD	11.677	2.395
	Median	23.44	1.51
	Q1, Q3	16.14, 37.33	0.00, 3.53
	Min, Max	12.97, 45.19	0.00, 6.87
2	N	10	10
	Mean	22.35	1.93
	SD	15.590	4.668
	Median	19.24	0.00
	Q1, Q3	9.93, 29.94	0.00, 1.37
	Min, Max	1.60, 53.89	0.00, 14.91
≥3	N	12	12
	Mean	19.46	1.39
	SD	8.774	2.105
	Median	17.63	0.00
	Q1, Q3	13.43, 23.78	0.00, 2.54
	Min, Max	7.98, 36.32	0.00, 6.07

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
PFIZER CONFIDENTIAL SDTM Creation: 03JUN2025 (15:54) Source Data: adabr Table Generation: 27NOV2025 (10:38)
(Data cutoff date : 29APR2025 Database snapshot date : 03JUN2025) Output File: ./nda1_cdisc/B78401005_IN_TJ_ERRATA/adabr_tjcat_t01

Figure 24 presents a scatter plot of the ABR of treated bleeds during the ATP versus during the OP by haemophilia type. The efficacy of marstacimab was consistent across the range of ABRs during the OP. One participant with Haemophilia B reported an ABR of 16.60 during the OP and an ABR of 14.91 during the ATP; this participant dose escalated at Visit 16 and following dose escalation, only reported 2 bleeds (ABR post-dose escalation: 2.73), both requiring on-demand treatment with bypass agent.

Figure 24: ATP versus OP ABRs for treated bleeds by Haemophilia type for inhibitor cohort with on-demand at OP-MITT set

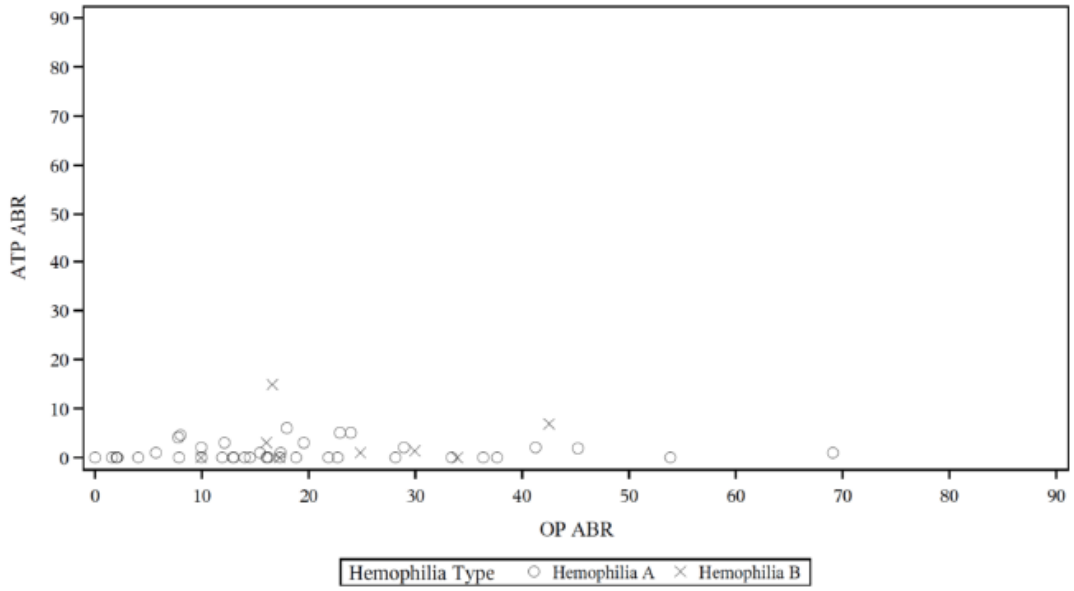


Table 33 presents a descriptive summary of ABR for treated bleeds by the mean ABR grouping (0 to <30, 30 to <60, ≥60) during the OP. The large reduction of ABR during marstacimab treatment versus on-demand treatment was consistent across the range of ABRs during the OP.

Table 33: Descriptive summary of ABR for treated bleeds by OP ABR grouping for inhibitor with on-demand at OP-MITT set (protocol B7841005_IN_CSR)

OP ABR Grouping	ABR[1] Descriptive Summary	OP ABR (N=48)	ATP ABR (N=48)
0 to < 30	N	39	39
	Mean	14.29	1.50
	SD	7.870	2.820
	Median	15.46	0.00
	Q1, Q3	7.98, 18.83	0.00, 2.03
	Min, Max	0.00, 29.94	0.00, 14.91
30 to < 60	N	8	8
	Mean	40.52	1.36
	SD	6.816	2.405
	Median	39.46	0.00
	Q1, Q3	35.13, 43.85	0.00, 2.02
	Min, Max	33.38, 53.89	0.00, 6.87
≥ 60	N	1	1
	Mean	69.10	1.01
	SD	NE	NE
	Median	69.10	1.01
	Q1, Q3	69.10, 69.10	1.01, 1.01
	Min, Max	69.10, 69.10	1.01, 1.01

1. ABR = annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.

B7841007: Phase 3 OLE Study

Study design

Study B7841007 is an open-label extension study to assess the long-term safety, tolerability, and efficacy of prophylaxis treatment with marstacimab in participants who did not require "Early Termination" from the pivotal Phase 3 Study B7841005. Interim results were available at the time of the initial marketing authorisation, which provided long-term data from the non-inhibitor cohort. Per study protocol amendment (23 Feb 2024), enrolment of two additional age groups (≥6 to <12 years of age and ≥1 to <6 years of age) from the ongoing parent paediatric Phase 3 Study B7841008 was enabled. Approximately 245 paediatric, adolescent and adult participants with severe Haemophilia A or moderately severe to severe Haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitors were planned to be enrolled in this study, continuing their prophylaxis treatment with once weekly subcutaneous injection of marstacimab at the dose established during participation in their respective parent study (B7841005 or B7841008).

All participants in B7841007 Study were provided the PFP device, intended for administration of marstacimab. Use of the PFS was permitted at the investigator's discretion for those participants who have difficulty with administration of the PFP. Additionally, participants were provided the PFS for use in this study in countries where the PFS is anticipated to be the only presentation available commercially.

The dosing regimen of marstacimab varies by age group. For adolescent and adult participants ≥12 years of age, a 300 mg loading dose of marstacimab is administered followed by 150 mg SC once weekly. For paediatric participants that are ≥6 to <12 years of age, the dosing regimen of marstacimab is a loading dose of 150 mg SC followed by 75 mg SC once weekly. Individual participants who meet protocol-specified dose escalation criteria based on weight and bleed events in either this protocol or during participation in the parent study, may have the dose increased to 300 mg (participants ≥12 years) or to 150 mg (participants ≥6 to <12 years) SC once weekly. Paediatric participants who reach 12 years of age and weighing at least 25 kg dose escalate to the ≥12 age group dosing regimen of 150 mg SC once weekly.

The study will continue until marstacimab is commercially available in each respective country or when the participants have completed 7 years of participation in Study B7841007, whichever occurs first. Therefore, the duration for each study participant will be variable. Additionally, commercial availability will likely vary by country and within study populations with initial approvals for adolescent/adults ages 12 to <75 years, followed by the younger age group.

At the time of the extension of indication procedure, an interim analysis with a cutoff date 30 May 2025, including data from adult and adolescent patients with and without inhibitors, was provided.

Study Objectives and Endpoints of the main study

Study objectives and endpoints are summarised in the below table. Evaluation of long-term efficacy was a secondary objective of the study.

Table 34: Study B7841007 Objectives and endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To determine the safety and tolerability of long-term treatment with marstacimab in severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) participants 12 to <75 years of age with or without inhibitors.	**Safety Endpoints** • AEs and SAEs. • Incidence and severity of thrombotic events. • Incidence and severity of thrombotic microangiopathy. • Disseminated intravascular coagulation/consumption coagulopathy. • Immunogenicity (incidence of ADA and clinically significantly persistent NAb against marstacimab). • Incidence and severity of injection site reaction. • Changes in vital signs. • Incidence of clinically significant laboratory value abnormalities. • Incidence of severe hypersensitivity and anaphylactic reactions.
Secondary:	**Secondary:**
• To evaluate long-term efficacy of treatment with marstacimab in severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) participants 12 to <75 years of age with or without inhibitors.	The following efficacy endpoints will be reported for each year of participation (Year 1, Year 2, etc): • Annualized rate of treated bleeding episodes. • Incidence of joint bleeds. • Incidence of spontaneous bleeds. • Incidence of target joint bleeds. • Incidence of total bleeds (treated and untreated). • Change in joints as measured by the HJHS. • Number of target joints. • Total coagulation factor or bypass consumption
• To evaluate the effect of marstacimab on HRQoL.	• Haem-A-QoL (≥17 years of age)/Haemo-QoL (Adolescents 12 to <17 years of age). • Health Utilities Measure (EQ-5D-5L).

Source: Module 5.3.5.2 B7841007 Interim CSR.

Number of Participants (planned and analysed):

This study was conducted at 64 sites in 23 countries: Argentina (1 site), Australia (1 site), Canada (3 sites), China (7 sites), Croatia (2 sites), France (1 site), Hong Kong (2 sites), India (4 sites), Israel (1 site), Italy (3 sites), Japan (7 sites), Korea, Republic of (3 sites), Mexico (1 site), Oman (2 sites), Russian Federation (1 site), Serbia (3 sites), Slovakia (1 site), South Africa (2 sites), Spain (4 sites), Taiwan (2 sites), Turkey (9 sites), the United Kingdom (1 site), and the United States (3 sites).

Overall, a total of 208 participants (inhibitor: 68 and non-inhibitor: 140) who met the eligibility criteria entered the treatment phase, including 155 participants from Study B7841005 and 53 participants from Study B7841008.

Among 208 participants who entered the study, 14 discontinued from study, of which 13 were from non-inhibitor group [9 (4.3%) withdrawal by subject, 4 (1.9%) due to adverse event, one (0.5%) "Other" reason of discontinuation].

Diagnosis and Main Criteria for Inclusion and Exclusion:

At the time of data cut off 30 May 2025, enrolled in this study were paediatric, adolescent, and adult participants (ages ≥6 to <75 years) with severe haemophilia A or moderately severe to severe haemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitors, as defined by the inclusion and exclusion criteria of the preceding pivotal Phase 3 Study B7841005 or paediatric Phase 3 Study B7841008. At the interim analysis cut off, data were available from adult and adolescent patients with and without inhibitors.

Duration of Study Intervention:

For participants aged ≥12 years, a loading dose of study intervention marstacimab (PF- 06741086) of 300 mg SC was administered followed by a dose of 150 mg SC QW. Participants ≥12 years weighing at least 50 kg who met protocol-specified dose escalation criteria based on bleeding events in either this protocol or during parent Study B7841005 or Study B7841008, could have the dose increased to 300 mg SC once weekly. Participants continuing from Studies B7841005 or B7841008 who have not received their weekly dose of study intervention (i.e., within 6 days after their scheduled dose for that dosing week) needed to administer a loading dose and then resume their prescribed dosing regimen.

Efficacy Analysis

The efficacy analyses were based on the Safety Analysis Set defined as all participants who received at least one dose of marstacimab. In the absence of a control group, descriptive summaries were provided without any hypothesis testing.

Results

Study population

Disposition

Participants in the inhibitor as well as the non-inhibitor cohort are included in this interim analysis, with a data cutoff of 30 May 2025. Participants who completed Study B7841005 or Study B7841008 and opted to be enrolled onto Study B7841007 on or before 30 May 2025 are included in the Study B7841007 dataset.

Of the 159 (inhibitor: 48, non-inhibitor: 111) participants who completed the parent Study B7841005, 155 (inhibitor: 47 and non-inhibitor: 108) were enrolled in Study B7841007 and 154 received at least one dose of marstacimab (safety set).

One non-inhibitor participant was randomized but withdrew consent and did not receive study drug.

Demographics and baseline characteristics

Participants enrolled from Study B7841005 (N=154) (all participants ≥12 years) and included in Study B7841007 safety analysis set were primarily Asian (79/154, 51.3% [inhibitor: 27, non-inhibitor: 52]) and White (65/154, 42.2% [inhibitor: 12, non-inhibitor: 53] participants). There were

9 Black/African American participant (9/154, 5.8%) (inhibitor: 8, non-inhibitor: 1). The race of 1 (0.6%) participant (non-inhibitor) was not reported.

The majority of participants were from Asia (71/154, 46.1% [inhibitor: 26, non-inhibitor: 45]) and Europe (42/154, 27.3% [inhibitor: 6, non-inhibitor: 36]).

Overall, among participants (N=154, inhibitor: 47, non-inhibitor: 107) from Study B7841005:

- 120 (77.9%) (inhibitor: 37, non-inhibitor: 83) participants had Haemophilia A and 34 (22.1%) (inhibitor: 10, non-inhibitor: 24) had Haemophilia B.
- 123 (79.9%) (inhibitor: 34, non-inhibitor: 89) participants were adults (≥18 years of age) and 31 (20.1%) (inhibitor: 13, non-inhibitor: 18) of participants were adolescents (12 to <18 years of age).
- 14 (29.8%) participants with inhibitors and 35 (32.7%) participants without inhibitors had no target joints at B7841005 study baseline.

All 154 participants were male (inhibitor: 47, non-inhibitor: 107) with a median age of 27.0 years (inhibitor: 23.0 years, non-inhibitor: 29.0 years) and individual values ranged from 12.0 to 75.0 years of age (inhibitor: 12.0 to 75.0 years, non-inhibitor: 13.0 to 66.0 years). The majority of participants (93/154, 60.4%) were in the 18 to 44 age range (inhibitor: 28, non-inhibitor: 65).

The median participant weight was 67.2 kg (range: 38.1 to 128.8 kg) and the median participant BMI was 22.9 kg/m^2 (range: 15.2 to 38.9 kg/m^2). The median participant height was 170.0 cm (range: 149.0 to 193.0 cm).

Most participants (130, 84.4%) (inhibitor: 44, non-inhibitor: 86) had normal renal function (eGFR ≥90 mL/min/1.73 m^2), while 21 (13.6%) (inhibitor: 2, non-inhibitor: 19) had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73 m^2) and none had moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73 m^2).

Efficacy results

ABR of treated bleeds

The model-based overall mean estimated ABR of treated bleeds was 2.44 (95% CI: 1.89, 3.13). For the inhibitor group, the model-based overall mean estimated ABR of treated bleeds was 1.19 (95% CI: 0.72, 1.95). For the non-inhibitor group, the overall estimated ABR of treated bleeds was 2.95 (95% CI: 2.21, 3.94). Additionally, the longitudinal trend across the first 3 years in both inhibitors and non-inhibitors group was similar.

Overall, during Year 1, Year 2, Year 3 and Year 4, there were 65 of 154 (42.2%) participants, 61 of 135 (45.2%) participants, 62 of 110 (56.4%) participants and 19 of 25 (76.0%) participants respectively, who had no treated bleeds.

Within the inhibitor group (N=47), in the first year of treatment, 29 of 47 (61.7%) participants observed zero bleeding events. This proportion progressively increased to 10 of 14 (71.4%) participants in Year 3 and 100% in the limited number of individuals with available data in Year 4 (N=3).

For the non-inhibitor group (N=107), in the first year of treatment, 36 of 107 (33.6%) of participants observed zero bleeding events. This proportion progressively increased to 52 of 96 (54.2%) participants in Year 3 and 16 of 22 (72.7%) participants in the limited number of individuals with available data in Year 4 (N=22).

Table 35: Summary of ABR for treated bleeds during year intervals for participants enrolled from B7841005 study safety analysis set (protocol B7841007_FS_IA3_CSR)

	Inhibitor					Non-Inhibitor					Overall				
ABR [1]	Year 1 (N=47)	Year 2 (N=32)	Year 3 (N=14)	Year 4 (N=3)	Overall (N=47)	Year 1 (N=107)	Year 2 (N=103)	Year 3 (N=96)	Year 4 (N=22)	Overall (N=107)	Year 1 (N=154)	Year 2 (N=135)	Year 3 (N=110)	Year 4 (N=25)	Overall (N=154)
Descriptive Summary															
n with no Treated bleeds (%) [3]	29 (61.7)	23 (71.9)	10 (71.4)	3 (100.0)	24 (51.1)	36 (33.6)	38 (36.9)	52 (54.2)	16 (72.7)	22 (20.6)	65 (42.2)	61 (45.2)	62 (56.4)	19 (76.0)	46 (29.9)
Mean (SD)	1.16 (1.942)	1.16 (2.366)	0.36 (0.617)	0.00 (0.000)	1.17 (2.012)	3.46 (7.050)	3.26 (8.809)	1.87 (3.204)	1.60 (2.758)	3.33 (6.913)	2.76 (6.058)	2.76 (7.821)	1.68 (3.041)	1.41 (2.634)	2.67 (5.943)
Median	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.00	0.00	0.94	1.00	1.00	0.00	0.00	0.79
(Q1, Q3)	(0.00, 2.00)	(0.00, 1.21)	(0.00, 1.00)	(0.00, 0.00)	(0.00, 1.18)	(0.00, 5.00)	(0.00, 3.00)	(0.00, 2.66)	(0.00, 4.81)	(0.35, 4.40)	(0.00, 3.00)	(0.00, 3.00)	(0.00, 2.00)	(0.00, 0.00)	(0.00, 2.63)
(Min, Max)	(0.00, 7.00)	(0.00, 9.33)	(0.00, 1.84)	(0.00, 0.00)	(0.00, 8.00)	(0.00, 50.73)	(0.00, 81.17)	(0.00, 18.01)	(0.00, 8.03)	(0.00, 50.73)	(0.00, 50.73)	(0.00, 81.17)	(0.00, 18.01)	(0.00, 8.03)	(0.00, 50.73)
Model-based Summary [2]															
Mean Estimate	1.20	1.16	0.45	NE	1.19	3.17	2.53	1.87	2.15	2.95	2.58	2.22	1.68	1.95	2.44
95% CI	(0.72, 2.02)	(0.49, 2.76)	(0.17, 1.19)	-	(0.72, 1.95)	(2.32, 4.32)	(1.87, 3.43)	(1.34, 2.60)	(1.01, 4.57)	(2.21, 3.94)	(1.96, 3.38)	(1.66, 2.97)	(1.22, 2.31)	(0.90, 4.23)	(1.89, 3.13)

Safety analysis set is defined as all participants who take at least 1 dose of study intervention.
Each treatment year represents a 365-day period. N indicates the number of participants receiving treatment within that year.
For Study B7841005, bleeding-related efficacy endpoints will consider all data irrespective of rescue medication use as well as dose modification. However, observations after discontinuation of treatment, if collected, or during the preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours) will not be included.
1. ABR= Annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.
2. Based on a negative binomial regression model without treatment and with a log link function, the model uses the number of bleeds as a response variable and log time on treatment as an offset variable to account for different duration on treatment.
3. Participants who discontinued treatment during the corresponding treatment period were considered as having treated bleeding events during that period.
CNA= Convergence Not Attained; NE= Not Estimated (N<5).
If N < 5, no model-based summary is presented; if the model did not converge, numbers are not presented.
PFIZER CONFIDENTIAL SDTM Creation: 19AUG2025 (08:16) Source Data: adabrmon Table Generation: 19AUG2025 (12:15)
(Data cutoff date : 30May2025 Database snapshot date : 27Jun2025) Output File: ./nda1 cdisc/B7841007 FS IA3 CSR/adhe s1001c
Table 14.2.1.1.1a Marstacimab is for Pfizer internal use.

Incidence of joint bleeds

The model-based overall mean estimate for the annualized incidence of joint bleeds was 1.83 (95% CI [1.40, 2.39]), and for the inhibitor group and non-inhibitor group was 0.87 (95% CI [0.49, 1.54]) and 2.21 (95% CI [1.64, 2.99])). Additionally, the longitudinal trend across the first 3 years in both inhibitors and non-inhibitors group was similar.

Incidence of spontaneous bleeds

The model-based overall mean estimate for the annualized incidence of spontaneous bleeds was 1.60 (95% CI [1.18, 2.16]), and for the inhibitor group and non-inhibitor group was 0.79 (95% CI [0.42, 1.48]) and 1.94 (95% CI [1.37, 2.74]), respectively. Additionally, the longitudinal trend across the first 3 years in both inhibitors and non-inhibitors group was similar.

Incidence of target joint bleeds

The model-based overall mean estimate for the annualized incidence of target joint bleeds was 1.02 (95% CI [0.68, 1.55]), and for the inhibitor group and non-inhibitor group was 0.46 (95% CI [0.20, 1.05]) and 1.26 (95% CI [0.78, 2.03]), respectively. Additionally, the longitudinal trend across the first 3 years in both inhibitors and non-inhibitors group was similar.

Incidence of total bleeds (treated and untreated)

The model based overall mean estimate for the annualized incidence of total bleeds (treated and untreated) was 3.41 (95% CI [2.74, 4.24]), and for the inhibitor group and non-inhibitor group was 2.91 (95% CI [1.89, 4.50]) and 3.60 (95% CI [2.79, 4.64]), respectively. Additionally, the longitudinal bleed control in both inhibitors and non-inhibitors group was maintained over time.

Haemophilia Joint Health Score (HJHS)

HJHS value continues to improve/stabilize over the course of the long term follow up to Year 3.

At Year 1 Day 360 (N=136), the mean change from overall baseline in the total HJHS score was -2.0 and -1.8 in the inhibitor (N=32) and non-inhibitor (N=104) participants, respectively.

At Year 2 Day 360 (N=109), the mean change from overall baseline in the total HJHS score was -1.4 and -2.0, in the inhibitor (N=13) and non-inhibitor (N=96) participants, respectively.

At Year 3 Day 360 (N=29), the mean change from overall baseline in the total HJHS score was -7.4 and -4.3, in the inhibitor (N=5) and non-inhibitor (N=24) participants, respectively.

Number of target joints

The durability of the effect of marstacimab on target joints beyond 12 months in parent Study B7841005 and up to an additional 43.1 months was maintained in long-term OLE Study B7841007 in participants with or without inhibitors.

A target joint is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period). Note that the endpoint of "incidence of target joint bleeds" counts *bleeding events* in "baseline" target joints identified in the screening period of the parent Studies B7841005 and B7841008 while "number of target joints" counts the number of *joints* where repeated bleeding occurred (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period). The number of target joints was derived from the eDiary for each year of participation (Year 1, Year 2, etc.).

The overall mean for the number of target joints was 0.09 for inhibitor group and 0.23 for non-inhibitor group. For Year 1, Year 2 and Year 3, the mean for the number of target joints was 0.04, 0.06 and none for the inhibitor group and 0.15, 0.09 and 0.04 for the non-inhibitor group, respectively.

Total coagulation factor consumption

For inhibitors group:

The mean total (per year) of total bypass product consumption was:

- 252.14 (SD: 175.574) IU/kg in the inhibitor group during the use of bypass agent aPCC.
- 316.91 (SD: 337.476) µg/kg in the inhibitor group during the use of bypass agent rFVIIa.

For non-inhibitors group:

The mean total (per year) of factor replacement consumption was 278.4 (SD: 700.59) IU/kg.

HRQoL outcomes

Haem-A-QoL (≥17 Years) and Haemo-QoL (Adolescents 12 to <17 Years)

In Study B7841005, physical health domain and total score were specified parameters within the statistical hierarchy. Overall, the treatment effect in the physical health domain and total scores in the Haem-A-QoL instrument was preserved in Study B7841007 for participants from Study B7841005 with or without inhibitors with clinically meaningful mean point change numerical improvement through Year 3.

At Year 1, Year 2, Year 3 (Day 360 Visit), across all participants, the mean point-change from the overall baseline for the physical health domain was -11.6 (N=90), -9.3 (N=75), and -9.8 (N=20),

respectively. The mean point-change from the overall baseline for the total score was -7.4 (N=90), -6.7 (N=75) and -7.1 (N=20), respectively.

At Year 1, Year 2, Year 3 (Day 360 Visit), for the inhibitor group, the mean change from the overall baseline for the physical health domain was -34.1 (N=17), -37.5 (N=6), and -5.0 (N=2) respectively. The mean change from the overall baseline for the total score was -18.2 (N=17), -27.3 (N=6) and -11.5 (N=2), respectively.

At Year 1, Year 2, Year 3 (Day 360 Visit), for the non-inhibitor group, the mean change from overall baseline for physical health domain was -6.3 (N=73), -6.9 (N=69) and -10.3 (N=18), respectively. The mean change from the overall baseline for the total score was -4.9 (N=73), -5.0 (N=69) and -6.6 (N=18), respectively.

Haemo-QoL for children (12 to <17 years of age)

A total of 22 participants (10 from the inhibitor and 12 from non-inhibitor group) completed this questionnaire at Year 1 Day 360. The mean change from overall baseline at Year 1 Day 360 for both the physical health domain and total scores was -15.1 and -8.9, respectively. The effect was maintained at Year 2 Day 180 (N=18) with a mean change from overall baseline of -22.2 and -10.3 for physical health domain and total score, respectively.

EQ-5D-5L

Across all participants who completed EQ-5D-5L at Year 1 Day 360, the mean change from overall baseline at Year 1 Day, Year 2, and Year 3 Day 360 in the index score was 0.09 (N=122), 0.04 (N=97), and 0.06 (N=27) respectively and the mean change from overall baseline in the EQ-VAS score in Year 1, Year 2 and Year 3 Day 360 was 6.74 (N=122), 3.13 (N=97), and 3.11 (N=27) respectively.

In inhibitor participants, the mean change from overall baseline at Year 1, Year 2, and Year 3 Day 360 in the index score was 0.20 (N=32), 0.25 (N=11), and 0.09 (N=5) while the mean change in the EQ-VAS score was 15.75 (N=32), 16.27 (N=11), and 10.00 (N=5).

In non-inhibitor participants, the mean change from overall baseline at Year 1 Day 360 in the index score was 0.05 (N=90), 0.01 (N=86), and 0.06 (N=22) while the mean change in the EQ-VAS score (n=90) was 3.53 (N=90), 1.45 (N=86), and 1.55 (N=22).

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Study B7841005 Summary of Efficacy for marstacimab for Participants With Inhibitors

Title: An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Haemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Haemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	
Study identifier	B7841005; EudraCT Number 2018-003660-31; NCT03938792
Design	One-way, cross-over, open-label, multi-centre

	Duration of Observation Phase (OP): Duration of Active Treatment Phase (ATP): Duration of follow-up:	6 months 12 months 30 days (if not enrolling in long-term extension study)	
Efficacy data presented in the Type II variation includes only the completed inhibitor cohort; efficacy data for the completed non-inhibitor cohort was included in the initial Marketing Authorisation Application (MAA).			
Hypothesis	**Inhibitor Cohort** Superiority of marstacimab prophylaxis during the Active Treatment Phase (ATP) as compared to on-demand bypassing agent treatment during the Observational Phase (OP).		
Treatment groups	Marstacimab (PF-06741086)	**12-month ATP following a 6-month OP:** Marstacimab administered 300 mg subcutaneously (SC) for the initial loading dose followed by 150 mg SC once weekly (QW). Individual participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding, may have had their dose increased to 300 mg SC QW • Inhibitor cohort: participants with inhibitors who were receiving prior on-demand treatment	
Endpoints and definitions	Primary Endpoint	Annualized bleeding rate (ABR) of treated bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for superiority versus on-demand.
	Secondary Endpoint	Incidence of joint bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for superiority versus on-demand.
	Secondary Endpoint	Incidence of spontaneous bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for superiority versus on-demand.
	Secondary Endpoint	Incidence of target joint bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for superiority versus on-demand.
	Secondary Endpoint	Incidence of total bleeds	Statistical testing was conducted for

		(treated and untreated)	marstacimab based on prespecified ordering for superiority versus on-demand.
Study Completion Date (Last Participant Last Visit [LPLV] for inhibitor cohort)	29 April 2025		

Results and Analysis

This study achieved its primary objective with marstacimab demonstrating superiority in efficacy over prior on-demand treatment as measured by ABR of treated bleeds for the prophylactic treatment of participants 12 to <75 years of age with severe haemophilia A or B with inhibitors.

Marstacimab prophylaxis demonstrated superiority (2-sided p-value <0.0001) over on-demand treatment as measured by the ABR of treated bleeds. Marstacimab prophylaxis demonstrated superiority (2-sided p-value ≤0.0001) over on-demand treatment and reduced the incidence of the following types of bleeds as compared to on-demand treatment: joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds (treated and untreated).

Marstacimab prophylaxis demonstrated superiority when compared with prior on-demand treatment for Haem-A-QoL physical health domain and total score, and EQ-5D-5L index score. The point estimate for change from baseline to 6 months for the EQ-VAS score numerically favoured marstacimab prophylaxis when compared to prior on-demand treatment, although lacking statistical significance.

Three participants with inhibitors and prior routine prophylaxis at OP were enrolled and completed the 12-month ATP. Their treated ABRs were numerically similar to participants with inhibitors and prior on-demand treatment at OP, with a reduction in treated bleeding episodes with marstacimab prophylaxis compared to prior prophylactic bypass treatment.

Analysis description	**Primary Analysis: ABR of treated bleeds**	
Analysis population and time point description	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab during the ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	
Descriptive statistics and estimate variability	Treatment group	Marstacimab
	Number of participants	Prior On-Demand: N=48
	Mean estimated ABR (95% Confidence Interval [CI])	ATP: 1.39 (0.85, 2.29) OP: 19.78 (16.12, 24.27)
	ABR Ratio (95% CI; p-value)	0.070 (0.042, 0.118; p<0.0001)
	Percentage reduction (95% CI)	93% (88.2%, 95.8%)
	Participants without treated bleeds, N (%)	ATP: 26 (54.2%) OP: 1 (2.1%)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand treatment.	
Analysis description	**Secondary analysis: Incidence of joint bleeds**	
Analysis population and time point description	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	
Descriptive statistics and	Treatment group	Marstacimab
	Number of participants	Prior On-Demand: N=48

estimate variability	Mean estimate (95% CI)	ATP: 1.10 (0.59, 2.04) OP: 15.15 (11.87, 19.34)
	Ratio estimate (95% CI; p-value)	0.072 (0.038, 0.138; p <0.0001)
	Participants without treated joint bleeds, N (%)	ATP: 31 (64.6%) OP: 4 (8.3%)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand treatment.	
Analysis description	**Secondary analysis: incidence of spontaneous bleeds**	
Analysis population and time point description	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	
Descriptive statistics and estimate variability	Treatment group	Marstacimab
	Number of participants	Prior On-Demand: N=48
	Mean estimate (95% CI)	ATP: 0.87 (0.53, 1.43) OP: 15.27 (12.07, 19.31)
	Ratio estimate (95% CI; p-value)	0.057 (0.035, 0.092; p <0.0001)
	Participants without spontaneous bleeds, N (%)	ATP: 28 (58.3%) OP: 5 (10.4)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand treatment.	
Analysis description	**Secondary analysis: incidence of target joint bleeds (treated)**	
Analysis population and time point description	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	
Descriptive statistics and estimate variability	Treatment group	Marstacimab
	Number of participants	Prior On-Demand: N=48
	Mean estimate (95% CI)	ATP: 0.79 (0.36, 1.74) OP: 6.30 (4.32, 9.20)
	Ratio estimate (95% CI; p-value)	0.126 (0.062, 0.256; p=0.0001)
	Participants without any bleeds (treated), N (%)	ATP: 36 (75.0%) OP: 20 (41.7%)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand treatment.	
Analysis description	**Secondary analysis: incidence of total bleeds (treated and untreated)**	
Analysis population and time point description	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	
	Treatment group	Marstacimab

Descriptive statistics and estimate variability	Number of participants	Prior On-Demand: N=48
	Mean estimate (95% CI)	ATP: 4.36 (2.65, 7.18) OP: 27.29 (22.54, 33.03)
	Ratio estimate (95% CI; p-value)	0.160 (0.102, 0.249; p <0.0001)
	Participants without any bleeds (treated and untreated), N (%)	ATP: 15 (31.3%) OP: 1 (2.1%)
Effect estimate per comparison	Post marstacimab administration for 12 months versus the 6-month OP with on-demand treatment.	
Source: Module 5.3.5.2 B7841005 Final Clinical Study Report (CSR)		

Immunogenicity

Table 37: Summary of ABR of treated bleeds (primary endpoint) by ADA status-inhibitor marstacimab safety set (primary endpoint) by ADA status-inhibitor marstacimab safety set (protocol B7841005_IN_CSR)

ABR[1]	Study B7841005 (N=51) ADA+ (N=10) n%	ADA- (N=41) n%
Descriptive Summary		
N[2]	10	41
Mean	1.15	1.51
SD	1.996	2.778
Median	0.00	0.00
Q1, Q3	0.00, 1.37	0.00, 2.03
Min, Max	0.00, 6.07	0.00, 14.91
n (%) with no treated bleeds[3]	5 (50.0)	22 (53.7)
Model-based Summary[4]		
Mean Estimate	1.16	1.46
95% CI	(0.42, 3.24)	(0.85, 2.53)

2.4.2. Discussion on clinical efficacy

In November 2024, a marketing authorisation for Hympavzi was issued for the indication of routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing >35kg, with severe HA or HB without inhibitors. With the current type II variation, the MAH submitted new clinical data from patients with inhibitors and seeks an extension of indication to include patients with haemophilia A or B with inhibitors into the label of Hympavzi.

The proposed agreed indication wording is:

Hympavzi is indicated 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

Design and conduct of clinical studies

The pivotal data in participants ≥12 years of age to support the extension of indication are derived from phase 3 study B7841005, which was a one-way cross-over, open-label, multi-centre study in adolescent and adult participants in patients ≥12 to <75 years of age with severe HA or severe HB with or without inhibitors. At the time of the initial marketing authorisation, only efficacy data from the non-inhibitor cohort were available. With the current submission, data from the completed inhibitor cohort were provided. Additionally, supporting data were submitted from the ongoing long-term safety and efficacy phase 3 study B7841007.

The pivotal study B7841005 had previously been assessed as part of the initial marketing authorisation, and reference is made to the Hympavzi EPAR for further assessment details on the general study design characteristics. Conduct of a combined study incorporating HA, HB, non-inhibitor, and inhibitor patient cohorts into a single study was considered acceptable from a regulatory perspective, in line with currently effective guidance on non-replacement therapies in haemophilia (EMA/CHMP/BPWP/518080/2024).

For individual participants the study duration was approximately 21 months, which included a 45-day screening period, a 6-month observational phase with on-demand treatment (and routine prophylactic treatment for a small subpopulation of inhibitor patients), a 12-month active treatment phase (initial loading dose of 300mg marstacimab followed by prophylactic weekly treatment with 150mg marstacimab), and a 1-month follow-up for safety monitoring. Participants with insufficient efficacy response were eligible for dose escalation after reaching prespecified criteria. Patients weighing at least 50 kg with 2 or more spontaneous (atraumatic) bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of coagulation FVIII or FIX over a 6-month period in the absence of confirmed FVIII or FIX inhibitors were eligible for dose escalation to weekly 300mg marstacimab. The design of the conducted single-arm study with an intra-patient comparison to a prospective run-in observational period is acceptable given the rarity of the disease and is in line with current guidance (EMA/CHMP/BPWP/518080/2024).

Eligible for enrolment into the study were adult or adolescent male participants 12 - <75 years of age with severe HA or moderately severe to severe HB. For enrolment into the inhibitor cohort, documentation of either high titre inhibitors or low titre inhibitors with FVIII or FIX recovery <60% of expected within the 6 months before enrolment were required. Additionally, based on a case-by-case evaluation, patients with documented *previous* inhibitors who did not quantitatively meet inhibitor threshold titres could be enrolled. Inhibitor patients previously on routine prophylaxis could be enrolled into a separate subgroup not eligible for the primary assessment. The generation of these supportive

data is acknowledged, as prophylaxis treatment with bypassing agents or non-factor replacement therapies is of interest due to the recent increase in available prophylactic treatment options for inhibitor patients. Patients with previous history of thrombotic events or at increased risk were excluded from enrolment. A corresponding warning regarding thromboembolic events, guidance in patients with a history of thromboembolic events as well as guidance on treating breakthrough bleeds is provided in section 4.4 of the SmPC.

Primary objectives and endpoints

The primary efficacy objective was to demonstrate superiority of marstacimab prophylaxis as observed over a 12-month active treatment phase compared to the 6-month observational on-demand phase prior to study intervention.

The primary efficacy endpoint was the ABR of treated bleeding events. The population summary utilised the ratio of the mean ABR (marstacimab prophylaxis vs. on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. The primary endpoint is clinically relevant.

Comparison to on-demand treatment is acceptable in haemophilia patients with inhibitors, given that on-demand treatment of bleeding episodes with bypassing agents is considered standard of care in patients with inhibitors.

The objective, choice of endpoints and chosen comparison with on-demand treatment are in line with guidance (EMA/CHMP/BPWP/518080/2024).

Estimand

The primary estimand was defined as the ratio (marstacimab vs. on demand) of the ABR regardless of rescue medication (coagulation factor replacement or bypass therapy), excluding data collected during preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours), dose modification and discontinuation of treatment. Using the treatment policy strategy for rescue medication and the while-on-treatment strategy for preventative treatment as defined for the primary estimand is considered relevant from a regulatory perspective.

For dose modification a treatment policy strategy would have been considered more appropriate, considering dose modification as part of the investigated treatment regimen. Finally, not including data after treatment discontinuation is not considered adequate. Instead, a treatment policy strategy would be of interest. This more relevant estimand, applying a treatment policy strategy for dose modification and treatment discontinuation, is investigated to some extent in the provided supplementary analyses.

Secondary endpoints

The set of bleeding-related secondary endpoints (ABRs of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds) had already been utilised in study B7841005 as part of the evaluation of efficacy in non-inhibitor patients, and is considered acceptable to provide additional clinically relevant data to supplement the primary endpoint also for the inhibitor patient cohort. In this regard it is noted that bleeding definitions were concise and well defined in the study protocol and were in accordance with ISTH guidelines (Blanchette 2014), which is acceptable.

Additional secondary endpoints included HJHS and HRQoL endpoints, which are generally considered informative. However, regarding PRO analyses a risk for bias in an unblinded study setting is noted, limiting their relevance. The overall set of secondary endpoints is considered acceptable. Reference is made to the Hympavzi EPAR, where additional assessment details are provided as part of the initial MA for Hympavzi.

Statistical methods

For the Inhibitor Cohort, the primary analysis was planned to estimate the ABR ratio of PF-06741086 prophylaxis over the routine on-demand treatment using a repeated measure negative binomial model via generalised estimating equation (GEE) approach. Superiority of PF-06741086 prophylaxis was considered demonstrated if the two-sided 95% CI for the ABR ratio (PF-06741086 prophylaxis/routine on-demand) lay below the pre-set threshold of 0.5. The analysis was to be based on dosed population, and missing values were not to be imputed. The bleeding counts in the analysis also were to include observations during the rescue medication use (in the form of coagulation factor replacement or bypass therapy) but to exclude observations after dose increase during PF-06741086 prophylaxis. All data during the preventative medical/dental treatment (plus 72 hours) were to be excluded. The analysis approach is considered adequate to estimate the primary estimand.

As discussed above, an estimand using a treatment policy strategy instead of a while-on-treatment strategy for the intercurrent events dose modification and treatment discontinuation is of regulatory interest. Aspects of this estimand are investigated by the supplementary analysis including data after dose increase and by the tipping point analysis assuming the bleed rate after treatment discontinuation being a multiple of the bleed rate observed during treatment. Upon request, the MAH clarified that there was only one subject with dose decrease and that temporary discontinuation periods were included in the ABR calculation for the primary estimand. Thus, the additionally requested supplementary analysis including data during dose modification is very similar to the pre-specified supplementary analysis including data after dose increase and of little relevance for the assessment.

In addition to the supplementary analysis, sensitivity analyses evaluating the impact of the carryover effect from the OP and of the seasonal effect were planned for. Correcting for the seasonal effect was performed by including only the portion of ATP that matches the calendar time of OP. Of note, the portion of ATP matching the calendar time of OP is always the second half of the ATP, i.e. the sensitivity analysis evaluates the long-term effect of marstacimab corrected for seasonality.

The secondary bleeding endpoints incidence of joint bleeds, incidence of spontaneous bleeds, incidence of target joint bleeds and the incidence of total bleeds (treated and untreated) were to be analysed analogously as the primary endpoint, which is considered adequate. There were several changes in the analysis plan for other secondary endpoints including PROs but as these endpoints are considered of little relevance for this open-label study, the modifications are not discussed further.

There were no subgroup analyses prespecified in the protocol or SAP. However, as the choice of subgroups finally analysed (Haemophilia type, age groups, race groups and geographic regions) is considered evident, no concern is raised.

The sample size calculation for the inhibitor cohort is considered adequate.

The type I error rate was controlled at 1-sided 0.025 level separately for the inhibitor cohort, the non-inhibitor cohort for the EU and the non-inhibitor cohort for regions outside of the EU. As discussed in scientific advice this approach is considered adequate for this setting.

The statistical analysis plan was amended five times with modifications relating e.g. to the definition of analysis sets and the approach for PROs. The modifications do not raise concerns.

Changes in the planned study conduct

A total of 7 protocol amendments were introduced, which were already incorporated into the study protocol at the time of the initial Hympavzi marketing authorisation and are further discussed there. Minor additional changes were introduced as protocol administrative changes.

Important protocol deviations were reported from 63% of participants and included issues regarding procedures/tests, the investigational product, informed consent, eligibility criteria, safety reporting, concomitant medications, and laboratory evaluations. 28% of participants had PRO questionnaires missing at 1 or more visits, which might have introduced bias and reduces the reliability of the PRO results.

Laboratory measures regarding factor VIII or IX activity as well as inhibitor concentration values analysed at one of the study site laboratories in China were considered unreliable at all timepoints due to lack of documentation and deviation from procedures. Therefore, factor VIII or IX activity values and inhibitor concentrations at screening and during the active treatment were replaced by historical and/or local laboratory sources. The MAH provided additional information regarding the enrolment process of the 19 patients affected by unreliable laboratory values upon request. Eligibility of these patients was confirmed using local factor inhibitor or historical values. All patients from the China sample had high inhibitor titres (≥5 BU/ml) at study visit 1, factor levels <1% (range 0.0-0.7), and received bypass therapy during the 6 months prior to study enrolment. Study eligibility for these patients therefore appears confirmed and did not raise concerns.

Efficacy data and additional analyses

Numbers analysed and baseline data

Overall, 47 patients with HA (including 11 HA adolescents) and 13 patients with HB (including 5 HB adolescents) were enrolled in the study, all of whom with severe disease. The mITT analysis set for the primary assessment consisted of 48 participants with previous on-demand treatment (40 HA patients and 8 HB patients) who entered the active marstacimab treatment period. Overall, 12 adolescent patients were included in the primary assessment, 9 with HA and 3 with HB.

It is noted that patient characteristics and demographics were summarised in the clinical documentation, per the "all analysis set" defined as all participants who received at least 1 prophylaxis or on-demand treatment at OP (and therefore including 9 patients who did not receive marstacimab treatment). In a comparison of the "all safety set" and the "safety set" (defined as those participants who received at least one dose of marstacimab), no significant differences between the analysis sets were noted, and no concerns arose regarding a potential patient selection bias from the OP to the ATP study period. Supportive evidence was generated in a very small set of inhibitor patients previously treated with prophylaxis (n=3, including 1 adolescent), which is acknowledged.

The patient population was relatively young, with 26.7% <18 and 58.3% 18-44 years of age. Only 9 patients were older than 44 years of age (including 1 patient aged 65-74 and 1 patient ≥75). Consequently, only very limited data from older patients are available from the inhibitor patient cohort. Regarding race, approximately 50% of participants were Asian, 33% were White, 14% were Black or African American.

A large proportion of the patient population had at least one target joint (70%), with 22% with ≥3 target joints at study entry, which is in line with target joint frequencies reported from other product developments and can be attributable to difficult-to-treat disease characteristics of haemophilia with inhibitors.

According to the indication wording, inhibitor patients irrespective of disease severity are proposed to be included in the label (in contrast to the non-inhibitor label, which is restricted to patients with severe disease). Indeed, only patients with severe disease were enrolled in the inhibitor cohort of the study. As per the guideline on the requirements for non-replacement therapies (EMA/CHMP/BPWP/518080/2024), gathering data from all severity subgroups to be included in the label is generally necessary, as benefit-risk considerations might differ between disease severity

subpopulations. However, factor activity levels do not necessarily correlate with the bleeding phenotype in inhibitor patients, and in the literature an increased risk for severe complications from bleeding is reported for mild and moderate haemophilia patients with inhibitors, with significantly increased mortality rates compared to non-inhibitor patients. Disease severity is considered less relevant in inhibitor patients as the presence of high-titre inhibitors makes FVIII/FIX ineffective regardless of endogenous factor levels. The proposed broad indication wording is furthermore in line with other comparable haemophilia therapies. Therefore, an indication wording for inhibitor patients irrespective of factor activity levels is considered acceptable. The patient population is also well-described in section 5.1 of the SmPC.

Regarding sample size, it is acknowledged that HA and even more so HB are rare diseases, leading to difficulties with recruitment of large sample sizes, which is particularly the case for HB patients with inhibitors. Nonetheless, the available sample size for inhibitor patients overall is small, with very low numbers for HB patients including adolescents (n=8, of whom 3 were adolescents). While a large proportion of HA patients had detectable inhibitors at screening (95%, 38/40), 50% (4/8) of the very limited sample of HB patients eligible for the primary assessment had a negative inhibitor status at screening. From the study protocol eligibility criteria, enrolment of these patients was possible based on historically documented inhibitor data even in the absence of quantitatively confirmed inhibitors at the time of screening, to be decided on a case-by-case basis. Upon request, the MAH confirmed that no maximum duration since the last positive historical inhibitor detection was specified in the study protocol. Indeed, some of the provided historical inhibitor values used for enrolment were very dated (>20 years). Nonetheless, no concern arises from the case-by-case patient selection process described by the MAH, and comparable strategies and inclusion criteria have been used in registrational studies of other product developments involving haemophilia patients with inhibitors. Reassuringly, all patients with inhibitors enrolled into study B7841005 were treated with bypassing agents when entering the study.

During the procedure, minor issues regarding the counting of baseline target joints for participants in study B7841005 were identified, which included data from 2 re-screened inhibitor participants and 1 re-screened non-inhibitor participant. No concerns arose from the minor changes introduced to results of the secondary endpoint of target joint bleeds in inhibitor patients.

Outcomes and estimation

In the primary analysis, superiority of marstacimab prophylaxis compared to on-demand treatment at OP was demonstrated. The mean ABR of treated bleeds was 1.39 (95% CI: 0.85, 2.29) during the active treatment period compared to 19.78 (95% CI: 16.12, 24.27) during the observational period with on-demand treatment, with a resulting estimated ABR ratio of 0.070 (95% CI: 0.042, 0.118). The proportion of patients who experienced 0 bleeds increased from 2.1% during the on-demand OP to 54.2% during marstacimab prophylaxis. The proportion of patients with ≥3 bleeds decreased from 87.5% during OP to 18.8% during marstacimab prophylaxis.

The distribution and frequency of intercurrent events do not raise concerns. As clarified during the assessment 50 out of 51 participants used rescue medication during OP compared to 23 participants during ATP. Preventative medication was used by 7 participants during OP and by 3 participants during ATP. Generally, it is reassuring that the bypass consumption during rescue and preventative treatment was decreased from 1444 (SD: 1797) IU/kg in the OP to 107 (SD: 67) in the ATP. There were four participants with dose increase and one participant with dose decrease. Of note, dose increase effected a decrease in mean ABR in these patients, in-line with results reported from dose escalation in non-inhibitor patients. As described above, there were three participants discontinuing the study.

In subgroup analyses, a relevant reduction in ABR of treated bleeds was observed across all subgroups analysed (HA, HB, adults, adolescents, ethnicity groups and geographic regions). The point estimates for subgroups indicated a significant and largely comparable effect size across all analysed subpopulations.

Supplementary and sensitivity analyses

Supplementary and sensitivity analyses for the primary assessment were prospectively defined and investigated the impacts of preventative infusions, dose escalation, treatment discontinuation, carryover effect from the OP, and seasonal effects.

The results of the sensitivity analyses were comparable to the results from the primary analysis. Compared to the primary assessment, a notable decrease in ABR was reported when matching the ATP portion to the calendar time of the 6 months of the observational period (0.048, 95%CI 0.026, 0.087). This effect may however to some extent also be attributable to extended treatment duration during the calendar-matched portion of the ATP, as lower ABR was reported during the second half of the ATP (0.79, SD 1.626) compared to the first half of the ATP (1.41, SD 2.687).

The provided sensitivity analyses were overall considered informative, supported the primary assessment, and provided additional robustness to the superiority claim over on-demand treatment.

Dose escalation

4/51 (7.84%) had their marstacimab dose escalated to 300mg QW. While the limited sample size is considered too small to enable drawing of robust conclusions, dose escalation effected a decrease in mean ABR in these patients, in-line with results reported from dose escalation in non-inhibitor patients.

The following recommendation has been added in section 4.2 of the SmPC: 'For patients on a maintenance dose of 300 mg: If one or more doses are missed, the missed dose should be administered as soon as possible, and then the usual 300 mg subcutaneous weekly dosing schedule (same schedule as prior to the missed dose or new schedule based on date of administration of missed dose) should be resumed.'

Inhibitor patients with routine prophylaxis at OP

Supportive evidence from a very small sample of patients with previous prophylaxis treatment at OP (n=3) indicated adequate efficacy in this patient population, mean ABR of treated bleeds were 7.61 (SD: 2.948) for prior prophylaxis at OP compared to 1.03 (SD: 1.020) during marstacimab prophylaxis in the ATP.

Secondary endpoint results

Superiority was demonstrated over previous on-demand treatment in all bleeding-related secondary endpoints, namely joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds, and the 95% CIs of the respective ratio estimates were below a prespecified "superiority margin" of 0.5. The respective ratio estimates were 0.072 (CI: 0.038, 0.138) for joint bleeds, 0.057 (CI: 0.035, 0.092) for spontaneous bleeds, 0.126 (CI: 0.062, 0.256) for target joint bleeds, and 0.160 (CI: 0.102, 0.249) for total bleeds, demonstrating a significant improvement in ABR compared to previous on-demand treatment. Additionally, considerable changes were noted both for increase in proportion of patients with 0 bleeds and decrease in proportion of patients with ≥3 bleeds for all secondary bleeding endpoints. Secondary bleeding-related endpoint results therefore supported the primary analysis.

From the haemophilia joint health score (HJHS), which was not part of the testing hierarchy, comparable results for previous on-demand treatment and marstacimab prophylaxis were reported.

Results from patient reported outcomes supported the primary assessment but are subject to uncertainty due to the open-label design, the amount of missing data and changes in the analysis plans during on-going study. Superiority of marstacimab over previous on-demand treatment was demonstrated for Haem-A-QoL physical health domain and total score, with respective median differences of -25.9 (95% CI: -37.5, -14.2) and -13.5 (95% CI: -19.8, -7.2). Superiority of marstacimab over previous on-demand treatment was demonstrated for EQ-5D-5L, with an estimated median difference of 0.1043 (95% CI: 0.0060, 0.2027). Superiority was not demonstrated for the EQ-VAS score, with an estimated median difference of 7.5 (-1.9, 17.0). Further support for the primary assessment was provided by results from PGIC-H, HAL2, and pedHAL, which reported improvement in patient global impression and self-perceived functional abilities.

Immunogenicity

No decrease in efficacy was evident from a small sample of patients with detectable ADAs (n=10). The mean estimated ATP ABR was 1.16 (95% CI: 0.42, 3.24) for ADA+ participants compared to 1.46 (95% CI: 0.85, 2.53) for ADA- participants.

Study B7841007 - OLE

For the OLE study B7841007 data from a total of 159 patients (49 inhibitor and 108 non-inhibitor patients) were available at the newly provided interim cut-off of 30 May 2025. 120 patients had HA (37 inhibitor, 83 non-inhibitor), and 34 patients had HB (10 inhibitor, 24 non-inhibitor). The currently available data continues to support the preservation of efficacy in patients treated with marstacimab weekly prophylaxis >12 months. For both inhibitor and non-inhibitor patients a tendency for ABR decrease over time (year 1-4) was noted. No study discontinuations due to lack of efficacy were reported at the interim analysis cut-off.

2.4.3. Conclusions on the clinical efficacy

Superiority of marstacimab weekly prophylaxis was demonstrated compared to previous on-demand treatment of haemophilia patients with inhibitors. The result was supported by secondary bleeding-related endpoints, haemophilic joint assessment, and QoL outcomes.

From a clinical efficacy perspective, the provided data support an extension of indication to HA/HB patients with inhibitors.

2.5. Clinical safety

Introduction

Hympavzi was licensed in November 2024 for the routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital FVIII deficiency, FVIII <1%) without FVIII inhibitors or severe haemophilia B (congenital FIX deficiency, FIX <1%) without FIX inhibitors.
In the safety database provided for the initial MAA, the most frequently reported AEs irrespective of causality were COVID-19, headache, contusion and hypertension. The most frequent treatment related AEs were injection site reactions and prothrombin fragment 1.2 increased. The AE profile was comparable in HA and HB and in those subjects who required a dose escalation. No thromboembolic events or severe hypersensitivity or anaphylactic reactions were observed during the clinical trials up to the presented data-cut off. Safety data from non-inhibitor as well as inhibitor cohorts were presented in a combined analysis to increase the size of the safety database.

Patient exposure

Safety data are available from the phase 3 study B7841005 for the inhibitor cohort (n=51; adults n=38, adolescents ≥12 to <18 n=13), encompassing 40 subjects with haemophilia A and 11 subjects with haemophilia B. Most patients rolled over into the long-term extension study B7841007 (haemophilia A: n = 37; haemophilia B: n = 10). In Studies B7841005/B7841007, overall, 51 participants with inhibitors ≥12 years of age had a median duration of treatment of 931.0 days, with a range of 259.0 – 1605 days and a total exposure of 125.1 patient years.

Safety data in adolescents are also available from the ongoing paediatric study B7841008 for 9 subjects ≥12 to <18 years of age in the inhibitor cohort (7 haemophilia A and 2 haemophilia B). To increase the safety pool, data from 15 participants in the non-inhibitor cohort (11 haemophilia A and 4 haemophilia B) have also been presented, which is endorsed. 12 subjects from the non-inhibitor cohort (haemophilia A n = 9; haemophilia B n = 3) and all 9 participants from the inhibitor cohort have already rolled over into the long-term extension study B7841007.

Adverse events

Table 38: Summary of TEAEs, SAEs and AESIs across age groups and inhibitor status

	Age ≥12 Years, Group 1 B7841005/B7841007 Inhibitors N=51	Age ≥12 to <18 Years, Group 3 B7841008/B7841007		Age ≥12 Years, Group 4 B7841005/B7841007 Non-Inhibitors N=116
		Inhibitors N=9	Non-Inhibitors N=15	
TEAEs (all-causality)	42 (82.4%)	7 (77.8%)	8 (53.3%)	99 (85.5%)
Grade 3 events	4 (7.8%)	0	1 (6.7%)	-
TEAEs (treatment-related)	16 (31.4%)	3 (33.3%)	2 (13.3%)	30 (25.9%)
SAEs	2 (3.9%)	0	0	24 (20.7%)
AESIs	29 (56.9%)	3 (33.3%)	3 (20.0%)	62 (53.4%)
ISRs	4 (7.8%)	1 (11.1%)	1 (6.7%)	11 (9.5%)
Thromboembolic events	0	0	0	1 (0.9%)

Participants are only counted once per treatment per event.

The integrated analysis of all-causality TEAEs from **participants with inhibitors ≥12** years of age enrolled in study B7841005/ B7841007 showed:

☐ In Study B7841005 (N=51) during ATP which represents the initial 12 months of exposure, the most frequently (≥10%) reported all-causality TEAEs were COVID-19 (11 participants, 21.6%) and upper respiratory tract infection (8 participants, 15.7%). The majority of TEAEs were mild/moderate in severity 39.2% of participants reported Grade 1 events, 27.5% of participants reported Grade 2 events). Grade 3 events were reported in 4 (7.8%) participants and included pyrexia, upper respiratory tract infection, haemophilic arthropathy, and rash (each reported in 1 [2.0%] participant).

☐ In Study B7841007(N=47) which represents exposure beyond the initial 12 months in the parent study to a maximum of 41.33 months, the most frequently (≥10%) reported all-causality TEAE was upper respiratory tract infection (5 participants, 10.6%). All events were mild or moderate in severity (17.0% of participants reported Grade 1 events, 27.7% of participants reported Grade 2 events) except for a Grade 3 event of haemophilic arthropathy in 1 (2.1%) participant.

☐ In Studies B7841005/B7841007 (N=51) where participant data was combined to present the entire marstacimab exposure up to a maximum of approximately 53.50 months at the intended dose, the most frequently (≥10%) reported all-causality TEAEs were COVID-19 and upper respiratory tract infection (both in 11 participants, 21.6%), and fibrin D dimer increased (6 participants, 11.8%). All events were mild or moderate in severity (33.3% of participants reported Grade 1 events, 41.2% of participants reported Grade 2 events) except for the following Grade 3 events reported in 4 (7.8%) participants (pyrexia, upper respiratory tract infection, haemophilic arthropathy, rash; each reported in 1 [2.0%] participants).

The integrated analysis of all-causality TEAEs from **participants with or without inhibitors ≥12 to <18** years of age enrolled in studies B7841008/B7841007 showed:

☐ In Study B7841008, in participants with inhibitors (N=9), the most frequently reported all-causality TEAEs (≥10%) were upper respiratory tract infection (2 participants, 22.2%), and joint injury, prothrombin fragment 1.2 increased, mispositioned teeth, device malfunction, catheter site pain, injection site pain, injection site urticaria, joint swelling, lower respiratory tract infection, fall, troponin I increased, nasopharyngitis, tonsillitis, and viral infection (each reported in 1 participant, 11.1%). In participants without inhibitors (N=15), the most frequently reported all-causality TEAEs (≥10%) were upper respiratory tract infection (3 participants, 20.0%) and upper respiratory tract infection (5 participants, 20.8%) overall. Overall, the majority of TEAEs were mild/moderate in severity (4 [44.4%] participants with inhibitors and 5 [33.3%] participants without inhibitors reported Grade 1 events, 2 [22.2%] participants with inhibitors and 1 [6.7%] participants without inhibitors Grade 2 events). Grade 3 events were reported in no participants with inhibitors and 1 (6.7%) participant without inhibitors (procedural haemorrhage).

☐ Study B7841007 represents exposure beyond 12 months in the parent study to a maximum of approximately 16.57 months for participants with inhibitors and approximately 14.23 months for participants without inhibitors at the intended dose. In participants with inhibitors (N=9) the most frequently reported all-causality TEAEs (≥10%) were asthma, fibrin D dimer increased, pyrexia, leukopenia, pain in extremity, vomiting, fall, tonsillitis (each reported in 1 participant, 11.1%) and participants without inhibitors or in the overall group did not report any TEAEs with a frequency ≥10%.

Overall, the majority of TEAEs were mild/moderate in severity (3 [33.3%] participants with inhibitors and 2 [16.7%] participants without inhibitors reported Grade 1 events, 2 [22.2%] participants with inhibitors and 1 [8.3%] participant without inhibitors reported Grade 2 events). No Grade 3 events were reported in participants with or without inhibitors.

☐ In Studies B7841008/B7841007, participants were combined to present the maximum exposure of 28.87 months for participants with inhibitors and 26.37 months for participants without inhibitors at the intended dose. In participants with inhibitors (N=9), the most frequently reported all-causality TEAEs (≥10%) were fall, upper respiratory tract infection (2 participants, 22.2%) and joint injury, asthma, fibrin D dimer increased, prothrombin fragment 1.2 increased, mispositioned teeth, device malfunction, pyrexia, catheter site pain, injection site pain, injection site urticaria, joint swelling, leukopenia, lower respiratory tract infection, pain in extremity, vomiting, troponin I increased, nasopharyngitis, tonsillitis, and viral infection (1 participant, 11.1%). In participants without inhibitors (N=15), the most frequently reported all-causality TEAEs (≥10%) were upper respiratory tract infection (3 participants, 20.0%), cough (2 participants, 13.3%). In the overall population (N=24), the most frequently reported all-causality TEAEs (≥10%) was the upper respiratory tract infection (5 participants, 20.8%). Overall, the majority of TEAEs were mild/moderate in severity (4 [44.4%] participants with inhibitors and 6[40.0%] participants without inhibitors reported Grade 1 events 3[33.3%] participants with inhibitors and 1 [6.7%] participants without inhibitors reported Grade 2 events). Grade 3 events were reported in no participants with inhibitors and 1 (6.7%) participant without inhibitors (procedural haemorrhage).

Treatment-related Adverse Events

Integrated analyses of treatment-related AEs from **participants with inhibitors ≥12** years of age enrolled in study B7841005/ B7841007 showed:

☐ In Study B7841005 (N=51) during ATP which represents the initial 12 months of exposure, the most frequently (PTs ≥5%) reported treatment-related AEs were fibrin D dimer increased (5 participants, 9.8%) and prothrombin fragment 1.2 increased (3 participants, 5.9%). When combining all ISRs PTs, 4 participants reported at least one ISR (7.8%). All treatment-related TEAEs were of Grade 1 or 2 severity except for a Grade 3 event in 1 participant (2.0%) (rash).

☐ In Study B7841007 (exposure beyond the initial 12 months in the parent study to a maximum of 41.33 months) and when combining both studies (total exposure up to a maximum of 53.5 months), no additional participants reported a treatment-related AE.

Integrated analyses of treatment-related AEs from **participants with or without inhibitors ≥12 to <18** years of age enrolled in studies B7841008/B7841007 showed:

☐ In Study B7841008, in participants with inhibitors (N=9), the most frequently reported treatment-related TEAEs (≥10%) were injection site pain, injection site urticaria, and prothrombin fragment 1.2 increased (each reported in 1 participant, 11.1%). In participants without inhibitors (N=15), no TEAEs were reported with frequency ≥10%, or in the overall group (N=24). All treatment-related AEs were mild in severity (2 [22.2%] participants with inhibitors and 2 [13.3%] participants without inhibitors reported Grade 1 events) and no participants with inhibitors or without inhibitors reported Grade 2 or 3 events.

☐ Study B7841007, represents exposure beyond 12 months in the parent study to a maximum of approximately 16.57 months for participants with inhibitors and approximately 14.23 months for participants without inhibitors at the intended dose. One additional treatment-related TEAE was reported corresponding to an AE of fibrin D dimer increased with mild severity, in one participant with inhibitors.

☐ In Studies B7841008/B7841007, participants were combined to present the entire marstacimab exposure up to a maximum exposure of 28.87 months for participants with inhibitors and 26.37 months for participants without inhibitors at the intended dose. In participants with inhibitors (N=9), the most frequently reported treatment-related TEAEs (≥10%) were injection site pain, injection site

urticaria, fibrin D dimer increased, prothrombin fragment 1.2 increased each reported in 1 (11.1%) participant. In participants without inhibitors (N=15) and in the overall group, no participants had TEAEs with a frequency ≥10%. All treatment-related AEs were mild in severity (3[33.3%] participants with inhibitors and 2[13.3%] participants without inhibitors reported Grade 1 events) and no participants with inhibitors or without inhibitors reported Grade 2 or 3 events.

Serious adverse event/deaths/other significant events

SAE

An integrated overview of SAEs across **participants with inhibitors ≥12 years** of age enrolled in study B7841005/ B7841007 showed:

☐ In Study B7841005 during ATP which represents the initial 12 months of exposure, SAEs were reported by 1 out of 51 (2.0%) participants (1 event of rash, considered treatment-related by the investigator).

☐ In Study B7841007 which represents exposure beyond the initial 12 months in the parent study to a maximum of 41.33 months, SAEs were reported by 1 out of 47 (2.1%) participants (1 event, haemophilic arthropathy). This SAEs was not considered treatment-related by the investigator.

☐ In Studies B7841005/B7841007 where participant data was combined to present the entire marstacimab exposure up to a maximum of approximately 53.50 months at the intended dose, SAEs were reported by 2 out of 51 (3.9%) participants; haemophilic arthropathy, and rash were each reported by 1 (2.0%) participant. The event of rash was considered treatment-related by the investigator.

An integrated overview of SAEs across **participants with or without inhibitors ≥12 to <18** years of age enrolled in studies B7841008/B7841007 showed that no SAEs were reported in any study, up to a maximum exposure of 28.87 months.

☐ In Studies B7841008/B7841007, participants ≥12 to <18 yrs of age were combined to present the maximum exposure of 28.87 months for participants with inhibitors and 26.37 months for participants without inhibitors at the intended dose, there were no SAEs reported by participants with or without inhibitors.

Deaths

There were no deaths in any of the marstacimab studies at the time of the data cut-off.

AESI

In **participants with inhibitors ≥12** years of age enrolled in studies B7841005/B7841007, 29 (56.9%) participants reported all-causality AESIs during the 12-month marstacimab treatment phase. The most frequently reported all-causality AESI was in the COVID-19 SMQ (COVID-19, 11 [21.6%] participants). The other frequently reported AESI (PTs ≥5%) was in the Hepatic Disorders SMQ (alanine aminotransferase increased, 3 [5.9%] participants). No thrombotic or embolic events were reported by participants treated with marstacimab.

AESIs in participants with inhibitors ≥12 years of age in the marstacimab clinical development are presented in Table 39.

Table 39: TEAEs of special interest for inhibitors cohort participants of age ≥12 years enrolled in studies B7841005 and B7841007 – marstacimab dataset (protocol B784_SCS_2025)

Number of Participants Evaluable for AEs Number (%) of Participants: by Event Type and Preferred Term	B7841005 (N=51) n (%)	B7841007 (N=47) n (%)	B7841005/ B7841007 (N=51) n (%)
With any AE of Special Interest	25 (49.0)	8 (17.0)	29 (56.9)
HAEMORRHAGES (SMQ)	4 (7.8)	2 (4.3)	5 (9.8)
Epistaxis	0	1 (2.1)	1 (2.0)
Haematuria	1 (2.0)	0	1 (2.0)
Haemophilic arthropathy	2 (3.9)	1 (2.1)	2 (3.9)
Urinary occult blood positive	1 (2.0)	0	1 (2.0)
HYPERSENSITIVITY (SMQ)	4 (7.8)	1 (2.1)	5 (9.8)
Asthma	0	1 (2.1)	1 (2.0)
Erythema	1 (2.0)	0	1 (2.0)
Pruritus	1 (2.0)	0	1 (2.0)
Rash	2 (3.9)	0	2 (3.9)
Stomatitis	1 (2.0)	0	1 (2.0)
ANGIOEDEMA (SMQ)	1 (2.0)	0	1 (2.0)
Urticaria	1 (2.0)	0	1 (2.0)
HYPERTENSION (SMQ)	2 (3.9)	0	2 (3.9)
Hypertension	2 (3.9)	0	2 (3.9)
ISCHAEMIC HEART DISEASE (SMQ)	1 (2.0)	0	1 (2.0)
Troponin increased	1 (2.0)	0	1 (2.0)
COVID-19 (SMQ)	11 (21.6)	0	11 (21.6)
COVID-19	11 (21.6)	0	11 (21.6)
GASTROINTESTINAL NONSPECIFIC DYSFUNCTION (SMQ)	2 (3.9)	3 (6.4)	5 (9.8)
Abdominal pain	1 (2.0)	0	1 (2.0)
Abdominal pain upper	0	1 (2.1)	1 (2.0)
Gastritis	1 (2.0)	1 (2.1)	2 (3.9)
Nausea	0	1 (2.1)	1 (2.0)
GASTROINTESTINAL NONSPECIFIC INFLAMMATION AND DYSFUNCTIONAL CONDITIONS	2 (3.9)	0	2 (3.9)
Diarrhoea	1 (2.0)	0	1 (2.0)
Vomiting	1 (2.0)	0	1 (2.0)
HEPATIC DISORDERS (SMQ)	3 (5.9)	2 (4.3)	3 (5.9)
Alanine aminotransferase increased	3 (5.9)	2 (4.3)	3 (5.9)
Aspartate aminotransferase increased	0	2 (4.3)	2 (3.9)
Gamma-glutamyltransferase increased	0	1 (2.1)	1 (2.0)
INJECTION SITE REACTIONS	4 (7.8)	0	4 (7.8)
Injection site erythema	2 (3.9)	0	2 (3.9)
Injection site haematoma	1 (2.0)	0	1 (2.0)
Injection site pain	2 (3.9)	0	2 (3.9)
Injection site pruritus	1 (2.0)	0	1 (2.0)
Injection site swelling	2 (3.9)	0	2 (3.9)

Participants are only counted once per treatment per event.
Totals for the number of participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different AEs within the higher level category.
Includes data from the first dose of marstacimab to the last study contact days.
MedDRA v28.0 coding dictionary applied.
Study B7841005(Non-Inhibitor Data cutoff : 17APR2023 , Inhibitor Data cutoff : 29APR2025); B7841007(Data cutoff : 30MAY2025); B7841008(Data cutoff : 26MAY2025);

In **participants with or without inhibitors ≥12 to <18** years of age enrolled in studies B7841008/B7841007, 6 (25.0%) participants reported all-causality AESIs. No AESI occurred in more than 1 (4.2%) participant. The most frequently reported all-causality AESI SMQs were ISR,

Gastrointestinal Nonspecific Dysfunction and Haemorrhages (2 [8.3%] participants each). No thrombotic or embolic events were reported by participants. AESIs in participants with or without inhibitors ≥12 to <18 years of age in the marstacimab clinical development are presented in Table 40.

Table 40: TEAEs of special interest for participants of age ≥12 to ‹18 years enrolled in studies B7841007- marstacimab dataset (protocol B784_SCS_2025)

Number of Participants Evaluable for AEs	Inhibitor			Non-Inhibitor			Overall		
Number (%) of Participants: by Event Type and Preferred Term	B7841008 (N=9) n (%)	B7841007 (N=9) n (%)	B7841008 / B7841007 (N=9) n (%)	B7841008 (N=15) n (%)	B7841007 (N=12) n (%)	B7841008 / B7841007 (N=15) n (%)	B7841008 (N=24) n (%)	B7841007 (N=21) n (%)	B7841008 / B7841007 (N=24) n (%)
With any AE of Special Interest	2 (22.2)	2 (22.2)	3 (33.3)	2 (13.3)	1 (8.3)	3 (20.0)	4 (16.7)	3 (14.3)	6 (25.0)
HAEMORRHAGES (SMQ)	0	0	0	1 (6.7)	1 (8.3)	2 (13.3)	1 (4.2)	1 (4.8)	2 (8.3)
Epistaxis	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Haematuria	0	0	0	0	1 (8.3)	1 (6.7)	0	1 (4.8)	1 (4.2)
Procedural haemorrhage	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
HYPERSENSITIVITY (SMQ)	1 (11.1)	1 (11.1)	1 (11.1)	0	0	0	1 (4.2)	1 (4.8)	1 (4.2)
Asthma	0	1 (11.1)	1 (11.1)	0	0	0	0	1 (4.8)	1 (4.2)
Injection site urticaria	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)
HAEMODYNAMIC OEDEMA, EFFUSIONS AND FLUID OVERLOAD (SMQ)	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)
Joint swelling	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)
ISCHAEMIC HEART DISEASE (SMQ)	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)
Troponin I increased	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)
GASTROINTESTINAL NONSPECIFIC DYSFUNCTION (SMQ)	0	1 (11.1)	1 (11.1)	1 (6.7)	0	1 (6.7)	1 (4.2)	1 (4.8)	2 (8.3)
Abdominal pain	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Vomiting	0	1 (11.1)	1 (11.1)	0	0	0	0	1 (4.8)	1 (4.2)
HEPATIC DISORDERS (SMQ)	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Alanine aminotransferase increased	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Aspartate aminotransferase increased	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Autoimmune hepatitis	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
INJECTION SITE REACTIONS	1 (11.1)	0	1 (11.1)	1 (6.7)	0	1 (6.7)	2 (8.3)	0	2 (8.3)
Injection site haemorrhage	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Injection site pain	1 (11.1)	0	1 (11.1)	0	0	0	1 (4.2)	0	1 (4.2)

Table 40: TEAEs of special interest for participants of age ≥12 to ‹18 years enrolled in studies B7841007- marstacimab dataset (protocol B784_SCS_2025) – con't

Number of Participants Evaluable for AEs	Inhibitor			Non-Inhibitor			Overall		
Number (%) of Participants: by Event Type and Preferred Term	B7841008 (N=9) n (%)	B7841007 (N=9) n (%)	B7841008 / B7841007 (N=9) n (%)	B7841008 (N=15) n (%)	B7841007 (N=12) n (%)	B7841008 / B7841007 (N=15) n (%)	B7841008 (N=24) n (%)	B7841007 (N=21) n (%)	B7841008 / B7841007 (N=24) n (%)
Injection site pruritus	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)
Injection site swelling	0	0	0	1 (6.7)	0	1 (6.7)	1 (4.2)	0	1 (4.2)

Participants are only counted once per treatment per event.
Totals for the number of participants at a higher level are not necessarily the sum of those at the lower levels since a participant may report two or more different AEs within the higher level category.
Includes data from the first dose of marstacimab to the last study contact days.
MedDRA v28.0 coding dictionary applied.
Study B7841005(Non-Inhibitor Data cutoff : 17APR2023 , Inhibitor Data cutoff : 29APR2025); B7841007(Data cutoff : 30MAY2025); B7841008(Data cutoff : 26MAY2025);
PFIZER CONFIDENTIAL Table Generation: 21AUG2025 (14:25) Output File: ./IACSR2025/B784 SCS 2025/adae s0311c
Table 14.3.1.5.1c Marstacimab is for Pfizer internal use.

Thromboembolic events

1 (0.9%, 1/116) thrombotic SAE (verbatim term: right subclavian vein thrombosis) was reported in a adult **male with haemophilia A in the non-inhibitor cohort of Study B7841007** (this participant was previously in Study B7841005).

There were no reports of embolic events for any participants of any age with or without inhibitors following marstacimab treatment across Studies B7841005, B7841008 or B7841007. At the time of the data cut, there was only the single event of thrombosis in the 1 non-inhibitor cohort participant mentioned above.

On December 22, 2025, Pfizer announced the death of a subject in OLE study B7841007. An adult patient with haemophilia A and inhibitors suffered a cerebral infarction and subsequent cerebral haemorrhage. The incident occurred while receiving weekly marstacimab prophylaxis and recombinant factor VIIa for bleeding management after minor surgery. This case highlights the potential thrombotic risk associated with TFPI inhibition, particularly in peri-operative settings and when used concomitantly with bypassing agents.

Dose modifications

An integrated overview of dose modification and temporary discontinuations across **participants with inhibitors ≥12** years of age enrolled in studies B7841005/B7841007 showed:

☐ In Study B7841005 during the ATP, which represents the initial 12 months of exposure, 10 (19.6 %) participants had dose reductions or temporary discontinuations due to AEs as follows: COVID-19 (7 [13.7%]) participants, and abdominal pain, viral upper respiratory tract infection, and rash (each reported in 1 [2.0] participant). The event of rash was considered treatment related.

☐ In Study B7841007 which represents exposure beyond the initial 12 months in the parent study to a maximum of 41.33 months, 2 (4.3 %) participants with inhibitors had dose reductions or temporary discontinuations due to AEs as follows: upper respiratory tract infection and haemophilic arthropathy, each in 1 (2.1%) participant. Neither of these events were considered treatment related.

☐ In Studies B7841005/B7841007 where participant data was combined to present the entire marstacimab exposure up to a maximum of approximately 53.50 months at the intended dose, 12 (23.5 %) participants had dose reductions or temporary discontinuations due to AEs: COVID-19 (7 [13.7%]) participants, and abdominal pain, viral upper respiratory tract infection, rash, upper respiratory tract infection and haemophilic arthropathy (each reported in 1 [2%] participant). The event of rash was treatment-related.

An integrated overview of dose modification and temporary discontinuations across **participants with or without inhibitors ≥12 to <18** years of age enrolled in studies B7841008/B7841007 showed:

☐ In Studies B7841008/B7841007 where participants were combined to present the maximum exposure of 28.87 months for participants with inhibitors and 26.37 months for participants without inhibitors at the intended dose, no participants with or without inhibitors ≥12 to <18 years of age had a dose reduction or temporary discontinuation due to AEs.

Laboratory findings

Apart from the unspecific activation of the coagulation system with increases of D-dimer and prothrombin fragment 1.2 which has already been evident in the non-inhibitor cohort assessed in the initial MAA, no additional findings were observed.

Immunogenicity

Adults and Adolescents (≥12 years; B7841005/B7841008/B7841007)

☐ In the pooled Studies B7841005/B7841008/B7841007, a total of 191 participants (60 inhibitor + 131 non-inhibitor cohort participants) were ADA-evaluable (i.e., had at least 1 ADA result). Out of the 191 ADA-evaluable participants, 135 participants were adults (≥18 years) and 56 were adolescents (≥ 12 to <18 years).

☐ Of the 191 ADA-evaluable participants, 3 participants (1 adolescent inhibitor cohort participant and 2 adult non-inhibitor cohort participants) had a positive ADA titre at baseline.

☐ Of the 191 ADA-evaluable participants, 43 participants (22.5% incidence) were ADA positive (+ve) (all treatment induced). Out of the 43 ADA+ve participants, 34 were adults (34 out of 135 adult participants; 25.2%) and 9 were adolescents (9 out of 56 adolescent participants; 16.1%). Out of the 43 ADA+ve participants, 28 were non-inhibitor (28 out of 131 non-inhibitor cohort participants; 21.4%) and 15 were inhibitor cohort participants (15 out of 60 inhibitor cohort participants; 25.0%).

☐ 9 of the 43 ADA+ve participants were NAb+ve (NAb incidence relative to ADA+ve participants [9/43] = 20.9%; NAb incidence relative to ADA-evaluable participants [9/191] = 4.7%). Out of the 9 NAb+ve participants, 7 were adults (7 out of 34 ADA+ve adult participants; 20.6%) and 2 were adolescents (2 out of 9 ADA+ve adolescent participants; 22.2%). Out of the 9 NAb+ve participants, 6 were non-inhibitor (6 out of 28 ADA+ve non-inhibitor cohort participants; 21.4%) and 3 were inhibitor cohort participants (3 out of 15 ADA+ve inhibitor cohort participants; 20.0%).

In the pooled Studies B7841005/B7841008/B7841007 for participants ≥12 years of age, ADA incidence was slightly higher in adults compared to adolescents; no relevant differences were seen between inhibitor and non-inhibitor cohort participants. No clinically relevant differences were observed in NAb incidences between the age groups or between inhibitor and non-inhibitor cohort participants.

☐ In the pooled Studies B7841005/B7841008/B7841007, ADA titres were low (maximum titre log10 value = 3.34, titre log10 cutoff = 1.53) and mostly seen by the first post-dose visit ie, Day 28 (23 out of 43 ADA+ve participants = 53.5).

☐ ADAs were transient (ADA positivity for <16 weeks at any time during the study) in 65.1% (28/43), persistent (ADA positivity for ≥16 weeks at any time during the study) in 32.6% (14/43), and indeterminate in 2.3% (1/43) of the ADA+ve participants, indicative of a transient ADA profile in the majority of the participants.

☐ Maximum duration of ADA persistence was approximately 1232 days (median of 278 days).

☐ At the study cutoff, there were 0 adult participants (last visit: Year 4 Day 180) and 1 inhibitor cohort adolescent participant (last visit: Year 3 Day 360) who were ADA+ve.

☐ All NAbs were treatment induced and titres were low (maximum titre log10 value = 2.26, titre log10 cutoff = 1.08). NAbs were transient (NAb positivity for <16 weeks at any time during the study) in 77.8% (7/9) and persistent (NAb positivity for ≥16 weeks at any time during the study) in 22.2% (2/9) of the NAb+ve participants, indicative of a transient NAb profile in the majority of the participants. Maximum duration of NAb persistence was 181 days (titer log10 range: 1.44 to 2.02, titre log10 cutoff = 1.08). No participants were NAb+ve at the study cutoff.

Overall, for all participants ≥12 years of age with and without inhibitors in the pooled Studies B7841005/B7841008/B7841007, ADA and NAb titers were low, transient in the majority of participants and resolved in all or most of the participants by study cutoff.

Among participants with inhibitors ≥12 years of age in Studies B7841005/B7841007, the model-based mean (95% CI) ABR of treated bleeds was 1.35 (0.57, 3.17) for participants who tested positive for ADA at any time during marstacimab treatment versus 1.20 (0.71, 2.02) in those who were negative throughout the study. In the 2 participants ≥12 years of age in Studies B7841005/B7841007 who tested NAb+ve, the ABR was 0.

Overall, ADA positivity had no impact on the incidence or severity of SAEs, TEAEs, or AESIs in participants with or without inhibitors ≥12 years of age. There was no notable pattern with regard to incidence of TEAEs reported in ADA+ve participants compared to ADA-ve participants. TEAEs were mild to moderate (Grade 1 or 2) for the majority of ADA+ve participants; incidence of TEAEs Grade 3 or higher was comparable between ADA+ve and ADA-ve participants. No deaths have been reported. No ADA+ve participant met the Sampson Criteria for anaphylaxis.

Safety in special populations

The observed safety profile was consistent across subgroups (haemophilia type, age, race, ethnicity, geographic region).

Renal Impairment

Clinical studies have not been conducted to evaluate the effect of renal impairment on marstacimab PK.

All patients with haemophilia A and B in the population PK analysis had normal renal function (N = 198; eGFR ≥90 mL/min/1.73 m2) or mild renal impairment (N = 25; eGFR of 60 to 89 mL/min/1.73 m2). Mild renal impairment did not affect the pharmacokinetics of marstacimab. No dose adjustment is recommended in patients with mild renal impairment.

No data are available on the use of marstacimab in patients with moderate or severe renal impairment.

Hepatic Impairment

Clinical studies have not been conducted to evaluate the effect of hepatic impairment on the PK of marstacimab.

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>ULN, AST>ULN). Mild hepatic impairment did not affect the PK of marstacimab. No dose adjustment is recommended in patients with mild hepatic impairment.

No data are available on the use of marstacimab in patients with moderate or severe hepatic impairment.

Elderly

No dose adjustments are recommended in patients over 65 years of age. There are limited data in patients over 65 years of age.

Safety related to drug-drug interactions and other interactions

As marstacimab is a monoclonal antibody which is expected to undergo the regular IgG catabolism, no PK interactions with other medicinal products are expected. However, PD interactions with other treatments aiming at the function of the coagulation system can be anticipated. Nonclinical data as well as clinical data from bleeding events treated with FVIIa or aPCC concentrates while being on marstacimab prophylaxis provide reassuring evidence on the safety of treating breakthrough bleedings with lowest possible effective doses of FVIIa or FEIBA, as prescribed in the clinical study protocols.

Discontinuation due to adverse events

An integrated overview of discontinuations across **participants with inhibitors ≥12 years** of age enrolled in studies B7841005/B7841007 showed:

☐ In Study B7841005 during the ATP, which represents the initial 12 months of exposure, 1 (2.0%) participant discontinued from study due to an AE of rash (considered treatment-related).

☐ In Study B7841007 which represents exposure beyond the initial 12 months in the parent study to a maximum of 41.33 months, no participants discontinued from study due to AEs.

☐ In Studies B7841005/B7841007 where participant data was combined to present the entire marstacimab exposure up to a maximum of approximately 53.50 months at the intended dose, 1 (2.0%) participant discontinued from study due to an AE of rash, which was considered treatment-related).

An integrated overview of discontinuations across **participants with inhibitors ≥12 to <18 years** of age enrolled in studies B7841008/B7841007 showed:

☐ Across Studies B7841008/B7841007, participants were combined to present the maximum exposure of 28.87 months for participants with inhibitors and 26.37 months for participants without inhibitors at the intended dose. No participants with or without inhibitors discontinued from study due to AEs.

Post marketing experience

Hympavzi received approval in 2024 in the EU 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.

There has been only one case of thrombosis (lower leg) reported post-marketing in an adult haemophilia A patient without inhibitors. Additionally, one event of transient ischemic attack was reported in an adult patient with HB in the. Both events resolved.

Hympavzi has been approved in 41 countries and is currently marketed in 8 countries. No new adverse drug reactions have been reported in patients without inhibitors post-marketing.

2.5.1. Discussion on clinical safety

The initial marketing authorisation for Hympavzi was granted in November 2024 for the routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital FVIII deficiency, FVIII <1%) without FVIII inhibitors or severe haemophilia B (congenital FIX deficiency, FIX <1%) without FIX inhibitors. With this variation, the MAH submitted additional data to support an indication in patients aged 12 years or older with haemophilia A or B with inhibitors. Safety data for adolescents ≥12 to <18 and adults with haemophilia A or B with inhibitors are available from the pivotal phase 3 study B7841005, from the ongoing paediatric study B7841008 and the long-term extension study B7841007.

Exposure

38 adults and 13 adolescents provided safety data in the above-mentioned studies, of whom 47 had HAwI and 13 had HBwI. In studies B7841005/B7841007, overall, 51 participants with inhibitors ≥12 years of age had a median duration of treatment of 931.0 days, with a range of 259.0 - 1605 days and a total exposure of 125.1 patient years. About 30% of those subjects were White. From the paediatric study B7841008, safety data are available from 24 adolescents, 9 with inhibitors and 15 without. A total of 2 patients aged >65 have been exposed to marstacimab prophylaxis, 1 with and 1 without inhibitors.

Adverse Events

In participants ≥12 years of age with inhibitors in studies B7841005 and B7841007 and participants ≥12 to <18 years with or without inhibitors in study B7841008, the most frequently (≥10%) reported all-causality TEAEs were COVID-19, upper respiratory tract infection and fibrin D dimer increased. Most events were mild or moderate in severity. The AE profile was generally comparable across studies and the different investigated haemophilia subtypes.

The most frequently (≥10%) reported treatment-related AEs were fibrin D dimer increased, prothrombin fragment 1.2 increased and injection site reactions. All treatment related AEs were mild or moderate in severity, except one event of rash in 1 participant in study B7841005.

SAEs

Two SAEs were reported, one event of rash (related) in study B7841005 and one event of haemophilic arthropathy (not related) in study B7841007. No SAEs were observed in paediatric study B7841008.

Deaths

No deaths were reported in any trial of the clinical development programme.

AESIs

In participants with inhibitors ≥12 years of age enrolled in studies B7841005/B7841007, 29 (56.9%) participants reported all-causality AESIs during the 12-month marstacimab treatment phase. The most frequently reported all causality AESI was in the COVID-19 SMQ (COVID-19, 11 [21.6%] participants). The other frequently reported AESI (PTs ≥5%) was in the Hepatic Disorders SMQ (alanine aminotransferase increased, 3 [5.9%] participants). No thrombotic or embolic events were reported by participants treated with marstacimab.

In participants with or without inhibitors ≥12 to <18 years of age enrolled in studies B7841008/B7841007, 6 (25.0%) participants reported all-causality AESIs. No AESI occurred in more than 1 (4.2%) participant. The most frequently reported all-causality AESI SMQs were ISR, Gastrointestinal Nonspecific Dysfunction and Haemorrhages (2 [8.3%] participants each). No thrombotic or embolic events were reported by participants.

One (0.9%, 1/116) thrombotic SAE (right subclavian vein thrombosis) was reported in a male with haemophilia A in the non-inhibitor cohort of Study B7841007.

Discontinuation due to an AE

One subject in the inhibitor cohort of study B7841005 permanently discontinued due to a grade 3 SAE of rash. One participant in the non-inhibitor cohort of extension study B7841007 discontinued marstacimab due to an event of subclavian vein thrombosis.

Special Populations

A total of 9 adolescents with HAwI and 4 adolescents with HBwI have been exposed to marstacimab in pivotal study B7841005. Further, 7 adolescents with HAwI and 2 adolescents with HBwI have been exposed to marstacimab in paediatric study B7841008. Additionally, 11 adolescents with HA and 4 with HB provided supportive data in the paediatric trial.

Only two subjects >65 years of age were included into the clinical development programme.

Laboratory evaluations

Apart from the unspecific activation of the coagulation system with increases of D-dimer and prothrombin fragment 1.2 which has already been evident in the non-inhibitor cohort assessed in the initial MAA, no additional findings were observed.

ADA

In the total population of the pooled Studies B7841005/B7841008/B7841007, ADA incidence was 22.5% (n=43) in 191 evaluable subjects. Of these 43 subjects, 20.9% (n=9) were positive for nAb. Most observed ADAs and nAbs were transient and nAbs were of low titre and did not influence efficacy or safety outcomes. No meaningful differences were obvious between inhibitor or non-inhibitor cohorts.

Late breaking news

On December 22, 2025, Pfizer announced the death of a subject in OLE study B7841007. A patient with haemophilia A and inhibitors suffered a cerebellar infarction and subsequent cerebral haemorrhage. The incident occurred while receiving weekly marstacimab prophylaxis and recombinant factor VIIa for bleeding management after minor surgery. This case highlights the potential thrombotic risk associated with TFPI inhibition, particularly in peri-operative settings and when used concomitantly with bypassing agents. The MAH provided comprehensive information regarding the fatal event of cerebral infarction followed by cerebral haemorrhage which was reported in a subject with HAwI in the perioperative setting after bilateral ureteral stent placement. Warnings and guidance on peri-operative management, concomitant use of bypassing agents, and monitoring requirements have been

introduced and/or further strengthened in Section 4.4 and 4.5 of the SmPC. Thromboembolic event is an important identified risk as part of the safety specifications of the Risk Management Plan (RMP), there are additional risk minimisation measure (patient card) and patients will be monitored in European Haemophilia registers (please see pharmacovigilance plan below).

2.5.2. Conclusions on clinical safety

Based on the submitted data in HAwI and HBwI patients ≥12 years of age derived from the pivotal trial B7841005, the open-label extension trial B7841007 and the paediatric trial B7841008, marstacimab appears to be generally well tolerated. The most common treatment-related AEs were fibrin D-dimer increased, prothrombin fragment 1.2 increased and injection site reactions. All treatment related AEs in subjects with inhibitors were mild or moderate in severity. One grade 3 treatment-related AE of rash was reported in a subject with HAwI in trial B7841005, which led to permanent discontinuation. No other discontinuations due to an AE occurred in subjects with haemophilia with inhibitors. No new safety signals emerged, and the observed safety profile is consistent with the safety findings in the initial marketing authorisation procedure.

Late breaking news: On December 22, 2025, Pfizer announced the death of a subject in OLE study B7841007. An adult patient with haemophilia A and inhibitors suffered a cerebral infarction and subsequent cerebral haemorrhage. The incident occurred while receiving weekly marstacimab prophylaxis and recombinant factor VIIa for bleeding management after minor surgery. This case highlights the potential thrombotic risk associated with TFPI inhibition, particularly in peri-operative settings and when used concomitantly with bypassing agents. Warnings and guidance on peri-operative management, concomitant use of bypassing agents, and monitoring requirements have been introduced and/or further strengthened in Section 4.4 and 4.5of the SmPC. Thromboembolic event is an important identified risk as part of the safety specifications of the Risk Management Plan (RMP), there are additional risk minimisation measure (patient card) and patients will be monitored in European Haemophilia registers (please see pharmacovigilance plan below).

From a clinical safety perspective, the submitted data are adequate to support the extension of indication to patients with haemophilia with inhibitors 12 years of age or older with a bodyweight of at least 35kg.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines' web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.2 with the following content:

Safety concerns

Important identified risks	Thromboembolism
Important potential risks	None
Missing information	None

Pharmacovigilance plan

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.

Risk minimisation measures

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:

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

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	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hympavzi is currently indicated for routine prophylaxis in adult and adolescent patients with severe HA and HB without inhibitors. With this extension of indication, the MAH provided new data to support inclusion of inhibitor patients into the label.

The proposed amended indication wording is: 'Hympavzi is indicated 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'

3.1.2. Available therapies and unmet medical need

Generally, treatment options for haemophilia patients with inhibitors include immune tolerance induction protocols with high doses of factor replacement products (for low-titre inhibitor patients), bypassing products, and non-factor replacement products. Treatment options for disease subtypes differ. For HA patients, available products include recombinant FVIIa, FEIBA, and the FVIII mimic emicizumab (Hemlibra). For HB patients, options are more limited, as FEIBA should be avoided in these patients, and since emicizumab is restricted to patients with HA. Recently the TFPI antagonist concizumab (Alhemo) received approval for routine prophylaxis of bleeding in adult and adolescent patients with HA and HB patients with and without inhibitors.

3.1.3. Main clinical studies

The pivotal data in participants ≥12 years of age to support the extension of indication are derived from phase 3 study B7841005, which was a one-way cross-over, open-label, multi-centre study in adolescent and adult participants in patients ≥12 to <75 years of age with severe HA or severe HB with or without inhibitors. At the time of the initial marketing authorisation, only efficacy data from the non-inhibitor cohort were available. With the current submission, data from the completed inhibitor cohort were provided. Additionally, supporting data were submitted from the ongoing long-term safety and efficacy phase 3 study B7841007.

3.2. Favourable effects

The primary analysis demonstrated superiority of marstacimab prophylaxis compared to on-demand treatment at OP in a mixed population of HA and HB patients with inhibitors. The mean ABR of treated bleeds was 1.39 (95% CI: 0.85, 2.29) during the active treatment period compared to 19.78 (95% CI: 16.12, 24.27) during the observational period with on-demand treatment, with a resulting estimated ABR ratio of 0.070 (95% CI: 0.042, 0.118).

In subgroup analyses, a reduction in ABR of treated bleeds was observed for all subgroups analysed, including HA, HB, adults, and adolescents.

The proportion of patients who experienced 0 bleeds increased from 2.1% during the on-demand OP to 54.2% during marstacimab prophylaxis. The proportion of patients with ≥3 bleeds decreased from 87.5% during OP to 18.8% during marstacimab prophylaxis.

In a small sample of patients eligible for dose escalation (n=4), dose increase to 300mg weekly marstacimab effected a decrease in mean ABR.

Prespecified sensitivity analyses investigated the impact of carryover, seasonal effects, dose escalation, and discontinuations, and provided support for the primary assessment.

Superiority of marstacimab prophylaxis over on-demand treatment at OP was demonstrated for all bleeding-related secondary endpoints (joint, spontaneous, target joint, and total bleeds).

3.3. Uncertainties and limitations about favourable effects

The available sample size was limited, particularly for HB patients with inhibitors in the primary assessment (n=8). The sample of patients with inhibitors receiving the escalated dosing regimen was very small (n=4). As stated in section 5.1. of the SmPC: 'there were no clinically relevant differences

in pharmacodynamic effects between haemophilia participants with and without inhibitors following weekly subcutaneous administration of marstacimab.'

3.4. Unfavourable effects

The most frequently observed all-causality TEAEs (≥10%) were COVID-19 and upper respiratory tract infections.

The most frequently observed treatment-related AEs (≥10%) were D-dimer increased, prothrombin fragment 1.2 increased and injection site reactions.

Most ADRs were of mild or moderate severity, apart from one event of grade 3 rash.

No thromboembolic events were observed in the inhibitor population. One event of subclavian vein thrombosis occurred in a subject with HA in extension study B7841007 and one event of lower leg thrombosis was reported in the post marketing setting in a patient without inhibitors.

One treatment related SAE of grade 3 rash was observed in one subject with HbwI. No deaths occurred in any of the clinical trials.

In the total population of the pooled Studies B7841005/B7841008/B7841007, ADA incidence was 22.5% (n=43) in 191 evaluable subjects. Of these 43 subjects, 20.9% (n=9) were positive for nAb. Most observed ADAs and nAbs were transient and nAbs were of low titre and did not influence efficacy or safety outcomes. No meaningful differences were obvious between inhibitor or non-inhibitor cohorts.

Late breaking news: On December 22, 2025, Pfizer announced the death of a subject in OLE study B7841007. An adult patient with haemophilia A and inhibitors suffered a cerebral infarction and subsequent cerebral haemorrhage. The incident occurred while receiving weekly marstacimab prophylaxis and recombinant factor VIIa for bleeding management after minor surgery. This case highlights the potential thrombotic risk associated with TFPI inhibition, particularly in peri-operative settings and when used concomitantly with bypassing agents. The MAH provided comprehensive information regarding the event of cerebral infarction followed by the fatal event cerebral haemorrhage which was reported in an adult subject with HAwI in the perioperative setting after flexible cytoscopic removal of bilateral ureteral double J (D-J) tubes under intravenous anesthesia. Warnings and guidance on peri-operative management, concomitant use of bypassing agents, and monitoring requirements have been introduced and/or further strengthened in Section 4.4 and 4.5 of the SmPC. Thromboembolic event is an important identified risk as part of the safety specifications of the Risk Management Plan (RMP), there are additional risk minimisation measure (patient card) and patients will be monitored in a post-authorisation safety study involving European Haemophilia registers (please see pharmacovigilance plan above).

3.5. Uncertainties and limitations about unfavourable effects

The database for patients suffering from haemophilia with inhibitors is small due to the rarity of the disease, especially HBwI.

Extremely limited data are available in subjects ≥65 years of age, therefore no dose adjustments are recommended in patients over 65 years of age (please see section 5.2 of the SmPC).

Very limited data in patients with renal and hepatic impairment. As stated in section 5.2 of the SmPC: 'Marstacimab is a monoclonal antibody and is cleared via catabolism rather than renal excretion and a change in dose is not expected to be required for patients with renal impairment as well as for patients with hepatic impairment.'

3.6. Effects Table

Table 41: Effects Table for Hympavzi, indication of routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35kg, with HA or HB with inhibitors

Effect	Short description	Unit	Marstacimab prophylaxis	Control (on demand)	Uncertainties / Strength of evidence	References
Favourable Effects						
ABR	PEP treated bleeds	Mean (95 % CI)	1.39 (0.85, 2.29)	19.78 (16.12, 24.27)	ABR ratio vs OD: 0.070 (95% CI: 0.042, 0.118)	Study B7841005
ABR HA population	Treated bleeds	Mean (SD)	1.08 (1.738)	18.99 (14.960)	ABR ratio vs OD: 0.055 (95% CI: 0.032, 0.094)	Study B7841005
ABR HB population	Treated bleeds	Mean (SD)	3.40 (5.198)	23.89 (10.943)	ABR ratio vs OD: 0.134 (95% CI: 0.049, 0.363)	Study B7841005
Unfavourable Effects						
Injection site reactions	Including pain, swelling, bruising, pruritus, erythema	%	B7841005/ B7841007: 7.8% B7841008/ B7841007 8.3%	-	small size of the safety database B7841005/ B7841007: n=51; B7841008/B7841007 : n=24	Clinical safety section 2.5
Anti-drug antibodies		%	B7841005, B7841007, B7841008: 22.5% (43/191)	-		Clinical safety section 2.5.
Neutralising antibodies		%	B7841005, B7841007, B7841008: 20.9% (9/43) of	-		Clinical safety section 2.5

Effect	Short description	Unit	Marstacimab prophylaxis	Control (on demand)	Uncertainties / Strength of evidence	References
			ADA+ subjects 4.7% (9/191) of total subjects			
Thrombo-embolic events		&	OLE B7841007 0.5 % (1 death)		Cerebellar infarction and subsequent cerebral haemorrhage	Clinical safety section 2.5

Abbreviations: ABR annualised bleeding rate, HA haemophilia A, HB haemophilia B, OD on demand, SD standard deviation

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Treatment with marstacimab led to a significant and clinically relevant reduction of bleeding episodes requiring treatment. A relevant reduction in ABRs was demonstrated for both HA and HB patients with inhibitors and point estimates for subgroups indicated a significant and largely comparable effect size across all analysed subpopulations.

Results of the primary assessment were robust as evaluated with informative sensitivity and supplemental analyses and were supported by results of a relevant set of secondary endpoints. From a very small sample of eligible patients who needed a dose increase, a reduction in the mean ABR was reported. Study results were overall in line with results previously reported from non-inhibitor HA and HB patients.

Numbers of patients were generally limited, with particularly low numbers of HB inhibitor patients in the primary analysis (n=8, including 3 adolescents). However, given the rarity of disease and particularly the rarity of HBwI, and the MoA independent of the presence of inhibitors, the overall number of included patients across subgroups, is considered sufficient.

Marstacimab was well tolerated in the study population. The submitted safety data in subjects with haemophilia with inhibitors confirmed the observed safety profile of marstacimab in patients with haemophilia A or B without inhibitors. The analysis of TEAEs, SAEs and AESIs as well as post-marketing data did not reveal any new safety signals. Due to a thromboembolic event observed in the perioperative setting as well as two further reports of TEEs in the post-marketing setting, the MAH has strengthened warnings and guidance provided in sections 4.4 and 4.5 of the SmPC. There are additional risk minimisation measure (patient card) and patients will be monitored in European Haemophilia registers (please see pharmacovigilance plan above).

3.7.2. Balance of benefits and risks

Efficacy has been demonstrated in haemophilia patients with inhibitors, from 12 years of age.

The observed safety profile is acceptable with safety outcomes in patients with HA or HB with inhibitors comparable to those in patients suffering from HA or HB without inhibitors.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Hympavzi is positive in the following indication: 'Hympavzi is indicated 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'

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with haemophilia A with factor VIII inhibitors or haemophilia B with factor IX inhibitors for Hympavzi, based on final results from study B7841005 and interim results from supportive study B7841007. Study B7841005 is an open-label study in adolescent and adult severe (coagulation factor activity ≤2%) with or without inhibitors comparing standard treatment to PF-06741086 (marstacimab) prophylaxis. Study B7841007 is an open-label extension study to evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis in severe (coagulation factor activity <1%) hemophilia A participants with or without inhibitors or moderately severe to severe hemophilia B participants (coagulation factor activity ≤2%) with or without inhibitors. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.2 of the RMP has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regards to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000226246 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Hympavzi is not similar to Roctavian, Altuvoct, Hemgenix, Idelvion and Alprolix within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR- Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMA/VR/0000304590