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EMA/464842/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Hypavzi

International non-proprietary name: Marstacimab

Procedure No. EMEA/H/C/006240/0000

Note

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
%CV	percent coefficient of variation
ABR	annualised bleeding rate(s)
ACCR	Accumulation ratio
ADA	anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
APCC	Activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	Active Treatment Phase
AUC	area under the concentration-time curve
AUC ₄₈	AUC time curve from time zero to 48 hours
AUC ₁₆₈	AUC time curve from time zero to 168 hours
AUC _{inf}	area under the concentration-time curve from 0 to infinity
AUC _{last}	area under the concentration-time curve from 0 to time of last measurable concentration
AUC _{ss}	area under the concentration-time curve at steady-state
AUC _{tau}	AUC time curve during a dosing interval
BID	Twice daily
BLQ	Below limit of quantification
BP	Blood pressure
BU	Bethesda Units
C1q	Complement component 1q
CBER	Center for Biologics Evaluation and Research
CDC	US Centers for Disease Control and Prevention

CDER	Center for Drug Evaluation and Research
CDRH3	third complementarity-determining region of the heavy chain
CDRL3	third complementarity-determining region of the light chain
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL/F	apparent clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{\max}	maximum observed concentration
$C_{\max,ss}$	maximum observed concentration at steady state
CNS	Central nervous system
CO	Clinical Overview
COVID-19	coronavirus disease 2019
CRA	Cytokine release assay
CRO	Contract Research Organisation
CSR	Clinical Study Report
CV	Cardiovascular
CWRES	Conditional weighted residuals
CYP	cytochrome p450
DC-T	dendritic cell-CD4 T-cell assay
DDI	drug-drug interaction
dPT	dilute prothrombin time
DVT	deep vein thrombosis
D180	Day 180
EBE	Empirical Bayes estimate
EC ₅₀	50% effective dose
ECG	electrocardiogram
ECL	electrochemiluminescence
eGFR	estimated glomerular filtration rate
EHL	extended half-life

EMA	European Medicines Agency
Emax	maximal effect
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Level version
EQ-VAS	EQ visual analogue scale
EU	European Union
F	bioavailability
Fc	Fragment crystallizable region of an antibody
FcgR	Fc gamma receptor
FEIBA	Factor Eight Inhibitor Bypassing Activity
FDA	Food and Drug Administration
FIH	first-in-human
FIX	Factor IX
FVIIa	Factor VII activated
FVIII	Factor VIII
FX	Factor X
FXa	Factor X activated
GLP	Good Laboratory Practice
GOF	Goodness of fit
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults (≥17 years of age)
Haemo-QoL	Haemophilia Quality of Life Questionnaire for Children (Adolescents 12 to <17 years of age)
HAL2	Haemophilia Activities List
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HJHS	Haemophilia Joint Health Score
HRQoL	health-related quality-of-life
HTC	Hemophilia Treatment Centers
IFN- γ /- γ	interferon gamma
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgG1	immunoglobulin G1

IgG4	Immunoglobulin G4
IHC	Immunohistochemical
IIV	Inter-individual variance
IL-6	interleukin 6
IM	intramuscular(ly)
IND	Investigational New Drug
INR	international normalized ratio
IPRED	Individual predictions
ISI	Integrated Summary of Immunogenicity
ISR	injection site reaction
ISR	incurred sample reanalysis
IU	international unit
IV	intravenous
IVM	Intravital Microscopy
IWRES	Individual weighted residuals
K	Clot formation time
K1	Kunitz domain 1
K2	Kunitz domain 2
K3	Kunitz domain 3
k_a	first-order absorption rate constant
K_D	dissociation constant
LC/MS	liquid chromatography/mass spectrometry
LDT	laboratory developed test
LLOQ	Lower limit of quantification
LPLV	last participant last visit
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MAD	Multiple ascending dose
MAD	Mutual Acceptance of Data
mITT	Modified Intent-to-Treat

N	total number, total sample size
n	number (subgroup or subpopulation)
NAb	neutralizing antibody
NCA	Non-compartmental
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
NONMEM	Non-linear mixed-effects modeling
OECD	Organisation for Economic Co-operation and Development
OD	on-demand
OLE	open-label extension
OP	Observational Phase
PBS	Phosphate buffered saline
PD	pharmacodynamic(s)
PDCO	Paediatric Committee (Committee for Medicinal Products for Human Use [CHMP] of European Medicines Agency [EMA])
pedHAL	Pediatric Haemophilia Activities List
PGIC-H	Patient's Global Impression of Change-Haemophilia
PF 1+2	prothrombin fragment 1 +2
PFP	pre-filled pen
PFS	pre-filled syringe
PI	principal investigator
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PMAR	Population Modeling and Analysis Report
PRED	Population predictions
PRO	patient-reported outcome
PT	(MedDRA) Preferred Term; prothrombin time
Q	Inter-compartmental clearance
QoL	quality of life
QD	Once per day

QW	once weekly
R	Dose dependent decrease in clotting time
rFVIIa	Activated recombinant Factor VII
rFVIII	Recombinant Factor VIII
RSE	Relative standard error
RU	Relative unit
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBS	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology
SCS	Summary of Clinical Safety
SD	standard deviation
SEM	Standard error of the mean
SHL	standard half-life
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SPR	Surface Plasmon Resonance
SS	Steady state
$t_{1/2}$	Half-life
TCR	Tissue Cross Reactivity
TEAE	treatment-emergent adverse event
TEG	Thromboelastography
TF	Tissue factor
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
TK	Toxicokinetic
T_{max}	time of occurrence of C_{max}

TMDD	Target Mediated Drug Disposition
TNF-a	tumour necrosis factor a
UK	United Kingdom
ULN	upper limit of normal
ULOQ	Upper limit of quantification
US	United States
Vc	central volume of distribution
Vp	peripheral volume of distribution
V _{ss}	steady state volume of distribution
VWH	von Willebrand Factor
Vz/F	apparent volume of distribution
WFH	World Federation of Hemophilia

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe Ma EEIG submitted on 6 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Hympavzi, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Marstacimab was designated as an orphan medicinal product EU/3/16/1752 on 14.10.2016 in the following condition: Treatment of haemophilia A.

Marstacimab was designated as an orphan medicinal product EU/3/23/2866 on 13.12.2023 in the following condition: Treatment of haemophilia B.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was removed from the Union Register of designated orphan medicinal products on 10 October 2024. More information on the COMP's review can be found in the orphan withdrawal assessment report published under the 'Assessment history' tab on the Agency's website: <https://www.ema.europa.eu/en/medicines/human/EPAR/hympavzi>

The applicant applied for 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:

- 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.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0443/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0443/2022 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance Marstacimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific Advice / Protocol assistance

The Applicant received the following Scientific Advice and Protocol Assistance on the development relevant for the indication subject to the present application:

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 fetal 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 enrollment 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.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Daniela Philadelphia

Co-Rapporteur: Robert Porszasz

The application was received by the EMA on	6 October 2023
The procedure started on	26 October 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 January 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	30 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	29 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 February 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 May 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	1 July 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 July 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 July 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 September 2024
The CHMP, in the light of the overall data submitted and the scientific	19 September 2024

discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Hympavzi on	
The CHMP adopted a report on similarity of Hympavzi with Alprolix, Idelvion, Roctavian and Hemgenix	19 September 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product	19 September 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. 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. Blood coagulation is achieved by a highly regulated cascade of plasma proteins, which ensures that bleeding can be rapidly stopped and that once bleeding is stopped, the cascade is shut down to prevent thrombosis. This regulation is achieved by 2 overlapping pathways, the extrinsic (initiation) and intrinsic (amplification) pathways, which converge in a final common pathway of coagulation.

The Applicant proposes the following indication: Hymepavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older 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

2.1.2. Epidemiology

Incidence

Globally, haemophilia A occurs at a rate of approximately 17.1 cases per 100,000 males⁷. 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 Centers (HTC) network, with an incidence rate at birth of 17.9 per 100,000 male births¹⁰. According to the US Centers for Disease Control and Prevention (CDC), approximately 400 boys are born with haemophilia A each year in the US⁹. 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)¹⁰.

Haemophilia B occurs globally at an annual rate of approximately 1 in 30,000 (3.33 per 100,000) male live births³ and the incidence rate in the US is 5.3 per 100,000 male births⁸. While the CDC doesn't 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 A⁸. 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 Kingdom¹⁰.

Prevalence

The prevalence (per 100,000 males) is 6.0 cases for severe haemophilia A, and 1.1 cases for severe haemophilia B¹². The current worldwide population of patients with a diagnosis of haemophilia A, as determined by the World Federation of Hemophilia (WFH) 2021 survey (representing data reported from approximately 7.14 billion persons or roughly 91% of the world population), is estimated to be 185,318 individuals. An estimated 37,998 individuals have a diagnosis of haemophilia B⁷.

Data from the 2021 WFH Annual Global Survey collected from 118 countries show that males represented 81% of haemophilia A cases, females represented 3% of haemophilia A cases, and gender unknown represented 5% of haemophilia A cases. For haemophilia B, males represented 79% of cases, females represented 6% of cases, with 5% with gender unknown (note that numbers do not add up to 100% as not all countries provided gender data)⁷.

Europe:

According to the WFH Annual Global Survey 2021, the reported number of patients with a diagnosis of haemophilia A (all severities) in various countries is as follows: United Kingdom (UK), n = 7,064; Germany, n = 3,793; France, n = 7,623; and the Netherlands, n = 1,376.⁷

For haemophilia B, the distribution of patients in Europe differs from that of haemophilia A. The WFH Annual Global Survey 2021 reported that the number of patients with a diagnosis of haemophilia B (all severities) in various European countries is as follows: UK, n = 1,607; France, n = 1,841; Poland, n = 477; and Ireland, n = 223.⁹

The prevalence at birth (per 100,000 males) is 24.6 and 24.0 cases for all severities of haemophilia A, and 10.2 and 8.6 cases for severe haemophilia A in the UK and in France, respectively.¹⁰

2.1.3. 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 PTT.¹

2.1.4. Clinical presentation, diagnosis

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. Blood coagulation is achieved by a highly regulated cascade of plasma proteins, which ensures that bleeding can be rapidly stopped and that once bleeding is stopped, the cascade is shut down to prevent thrombosis. This regulation is achieved by 2 overlapping pathways, the extrinsic (initiation) and intrinsic (amplification) pathways, which converge in a final common pathway of coagulation.

Individuals with haemophilia A have a FVIII activity level below the normal range^{4,5}, while those with haemophilia B have a FIX activity level below the normal range. Severity of haemophilia A or B is defined into 3 categories based on circulating FVIII or FIX activity levels in the plasma, each of which is characterised by different bleeding profiles as presented in Table 1.

Table 1: Relationship of bleeding to factor activity level for Haemophilia A and B

Severity	Clotting Factor Level	Bleeding Episodes
Severe	<1% of normal (<1 IU/dL)	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1% to 5% of normal (1 to 5 IU/dL)	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5% to <40% of normal (5 to 40 IU/dL)	Rare spontaneous bleeding; severe bleeding with major trauma or surgery

Source: WFH Guidelines⁸

The most common haemophilia bleeds are prolonged spontaneous and/or traumatic bleeding within the musculoskeletal system and joints, as well as in the muscle and mucosal soft tissues. While less common, some types of bleeds, including intracranial and gastrointestinal bleeds, can be life-threatening. An individual's bleeding phenotype is the result of their genotype, joint health status and behaviour. Even among patients with severe haemophilia there can be considerable heterogeneity in bleeding phenotypes⁶.

2.1.5. Management

Treatment of haemophilia is primarily through replacement of the missing FVIII or FIX. The replacement factor products are commonly standard half-life (SHL) or extended half-life (EHL) recombinant factor products, but plasma-derived products of various purities are still in use. Treatment with the replacement coagulation factor can either be episodic, treating bleeding episodes on-demand as they occur, or prophylactic, preventing bleeding episodes by a regular schedule of FVIII or FIX infusions to maintain factor levels in a range >1%. Significant evidence exists that prophylactic treatment prevents bleeding episodes and the associated joint damage that is a major morbidity in haemophilic patients.^{11,12,13,14,15}

Due to the relatively short half-lives of FVIII and FIX, effective prophylactic treatment in patients without inhibitors may require frequent intravenous (IV) administration, with the most frequent administration being every 2 days for SHL FVIII products, and up to twice weekly for SHL FIX products.^{6,13,14,15} The recent development of EHL factor replacement products have helped reduce treatment burden for patients with haemophilia by lowering prophylactic infusion rates and maintaining higher trough levels.^{16,17,18} However, despite the approval of newer EHL products, patients still may require regular factor replacement IV infusions at frequencies ranging from twice weekly to once every 2 weeks.^{23,24}

Emicizumab (Hemlibra) is a bi-specific antibody that bridges activated coagulation Factor IXa and Factor X (to replace the function of missing activated FVIII). Hemlibra received approval by the EMA on 23 February 2018 for "routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors", "Hemlibra can be used in all age groups"²² and on 11 March 2019 received approval for "routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors", and is currently approved for once weekly (QW) administration for the first 4 weeks, followed by SC administration weekly, or every 2 or 4 weeks.^{23,24}

Several newer treatments for haemophilia A or B are available in some markets or have submissions currently under regulatory review. Hemgenix (etranacogene dezxaparvovec) is a gene therapy treatment conditionally approved in the EU for treatment of adults with haemophilia B.^{25,26} Roctavian (valoctocogene roxparvovec) is a gene therapy treatment that has been conditionally approved in the EU for the treatment of haemophilia A.²⁸ Alhemo (concizumab) is a new monoclonal humanised IgG4 antibody that targets the K2 domain of TFPI. Concizumab was approved in Canada in March 2023²⁹ and Australia in July 2023³⁰ for use in

haemophilia B patients with inhibitors and was approved in Canada in July 2023 for use in haemophilia A patients with inhibitors.³¹ Concizumab is under regulatory review in the US and EU.

2.2. 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 intended for routine prophylaxis of bleeding episodes in patients 12 years of age and older 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.

The recommended dose for patients 12 years of age and older, weighing at least 35 kg, is an initial loading dose of 300 mg by subcutaneous (SC) injection followed thereafter by 150 mg by subcutaneous injection once weekly.

Marstacimab drug product is a colourless to light yellow solution provided at pH 5.8 in a strength of 150 mg/mL for subcutaneous injection. Marstacimab is provided as prefilled syringe or pen. prefilled syringe is supplied as a single dose pre-filled syringe (Type I glass) with a plunger stopper (chlorobutyl elastomer) and a stainless steel 27 gauge, ½ inch staked needle with a needle shield (thermoplastic elastomer). The drug product contains no preservative. Marstacimab prefilled pen is a single dose, disposable prefilled pen designed to contain a 150 mg/mL marstacimab prefilled syringe for subcutaneous injection. The final assembled marstacimab pen consists of a syringe inside the pen made from Type I glass with a plunger stopper (chlorobutyl elastomer) and a stainless steel 27 gauge, ½ inch staked needle with a needle shield (thermoplastic elastomer). The label is wrapped around the body of the pen.

2.3. Type of Application and aspects on development

Scientific advice was provided by CHMP during several protocol assistance procedures for non-clinical and clinical topics, please see section 1.6.

2.4. Quality aspects

2.4.1. Introduction

The finished product (FP) is presented as solution for injection containing 150 mg/mL of marstacimab as active substance (AS). Other ingredients are: Disodium edetate, L-Histidine, L-Histidine monohydrochloride, Polysorbate 80 (PS80), sucrose, water for injections. The product is available in a prefilled syringe and a prefilled pen containing 1 mL solution for injection.

2.4.2. Active Substance

2.4.2.1. General Information

Marstacimab (INN) is a new active substance for the treatment of haemophilia A and haemophilia B. It is a recombinant human monoclonal IgG1 lambda antibody directed against the Kunitz 2 (K2) domain of tissue factor pathway inhibitor (TFPI) and produced in Chinese Hamster Ovary cells (CHO). The Applicant described the features of the antibody, its glycosylation, disulfide bonds and modifications to minimise Fc effector functions. The annotated primary amino acid sequence and the theoretical and experimental molecular mass is presented. Molecular formula as well as the element number of cysteine residues and disulfide bonds are listed.

2.4.2.2. Manufacture, process controls and characterisation

Manufacturers and GMP

The active substance is manufactured at Wyeth BioPharma, Division of Wyeth Pharmaceuticals LLC, 1 Burt Road, Andover, MA 01810, USA. All relevant GMP certificates are valid according to EudraGMDP database. QP declaration concerning GMP compliance of the active substance manufacture has been presented.

Description of Manufacturing Process and Process Controls

The manufacturing process for marstacimab active substance uses a recombinant Chinese hamster ovary (CHO) cell line that contains the DNA encoding the sequence for marstacimab and is grown in suspension culture. Chemically defined, animal-derived component-free media is used. Upon thawing of a working cell bank (WCB) vial, the cell culture is expanded in several steps from shake flasks/bags to a seed bioreactor. Cells from the seed bioreactor are then used as inoculum for a production bioreactor. The duration of an inoculum/campaign can vary but cannot exceed the established limit of *in vitro* cell age (LIVCA). A production bioreactor culture is harvested and clarified by centrifugation and depth filtration to remove cells and debris.

Following the harvest step, the pool is processed by a Protein A affinity chromatography step, a low pH virus inactivation step, and an anion exchange (AEX) chromatography step. The material is then processed through a virus retaining filter followed by concentration and buffer exchange in an ultrafiltration/diafiltration (UF/DF) step. The final formulation of active substance is followed by final filtration (0.2 µm), filling, and freezing.

Overall, sufficiently detailed flow charts were provided, and the manufacturing process is appropriately described. Critical and non-critical process parameters (CPP, non-CPP) and critical material attributes (CMA) and their established acceptable range as well as in-process tests (IPCs) are listed for every process step.

1 Control of materials tails of compendial and non-compendial raw materials are provided. Raw materials used for cell culture and purification process are listed with their respective quality standard and their intended use. Acceptable acceptance criteria are provided for the non-compendial raw materials. The composition of the cell culture media is described. Description of the filters and chromatography resins are provided. Overall, the provided information is sufficient.

The construction of the expression plasmid and their genetic elements are described in sufficient detail. The expression plasmid used for transfection was confirmed by sequencing. The information provided on origin and history of the CHO cell line and generation of the cell line clone is satisfactory. The host cell bank was adequately tested for contaminants. Chemically defined animal component-free medium was used to prepare the host cell bank.

A two-tiered cell bank system consisting of MCB and WCB has been established in accordance with ICH Q5D and GMP requirements. The cell banking system is adequately described with sufficient details on manufacture and storage of the MCB and WCB. Vials of both MCB and WCB are stored at multiple sites.

The cell banks have been adequately characterised. The Applicant has established a LIVCA from the MCB, phenotypic stability and comparability was confirmed for MCB, WCB and end of production (EOP) LIVCA cells. MCB and WCB stability is monitored; the proposed intervals are acceptable. A protocol for introduction of future WCBs has been included and considered acceptable.

In conclusion, the characterisation of the cell banks satisfactorily demonstrates identity, purity, suitability, and genetic stability.

Control of critical steps and intermediates

Details of process controls and CPPs have been provided. The process controls for cell culture and harvest include a combination of CPPs, non-CPPs, CMAs, and in-process tests. Operational parameter results outside control limits will be investigated.

In the upstream process, IPCs are established over the whole cell culture process.

In the downstream process, tests for bioburden and endotoxin are performed throughout the purification process. The purification process contains virus clearance and inactivation steps.

Overall, a holistic approach to the control strategy has been taken, where both active substance and finished product elements were considered in totality to ensure final finished product quality through shelf-life. For both cell culture/harvest and the downstream purification processes, the process controls include a combination of critical process parameters (CPP), non-critical process parameters (non-CPP), critical material attributes (CMA), and in-process tests. Overall, the control strategy in terms of CPPs and process controls is considered acceptable to ensure adequate control of the active substance manufacturing process. Hold times are supported by appropriate data.

Process Validation

Process performance qualification (PPQ) of the marstacimab commercial manufacturing process has been performed. Pre-defined acceptance criteria for performance were presented for the upstream and downstream processes. All PPQ batches met the pre-defined acceptance criteria when run within defined process parameters and met the release acceptance criteria, demonstrating the adequacy of the manufacturing process controls for consistent batch production. Overall, it is agreed that the PPQ showed that the manufacturing process is able to consistently produce active substance with predefined quality. The control strategy proved to be effective. Deviations were appropriately followed up.

Impurities

Removal of host cell-derived DNA and protein as well as process-derived and media-derived impurities has been demonstrated.. The results from the PPQ batches showed consistent capability of the purification steps to remove such impurities.

At the Active Substance level, all impurities were in a range that does not pose a safety concern.

To conclude, validation of the removal of impurities was appropriately performed and no issues are raised.

Hold times

In-process hold times to demonstrate biochemical stability were validated in small scale models representative of the commercial scale manufacturing, which is acceptable. The hold-times with respect to microbiological control were demonstrated on all PPQ batches. Overall, the in-process hold times for the commercial process were appropriately established and no issues are raised.

Column and Membrane Studies

Resin lifetime was appropriately established at small-scale and an acceptable protocol for monitoring resin lifetime at commercial scale was provided. For UF/DF membrane lifetime a concurrent validation protocol will be executed at commercial scale, which is acceptable. Overall, establishment of resin and membrane lifetime is appropriate.

Reprocessing

Reprocessing has been appropriately evaluated at small-scale for both filters and an appropriate protocol was provided to confirm reprocessing at commercial scale in case it is needed in the future. Overall, the Applicant's strategy to implement reprocessing is accepted.

Shipping validation

The shipping validation supports shipment of marstacimab active substance in the container closure was provided.

Manufacturing Process Development

Manufacturing-scale runs and process characterisation studies, including design of experiments (DoE) studies, using scale-down models of individual unit operations has been applied to establish an understanding of the marstacimab manufacturing process.

Comparability Assessment

Comparability assessments have been performed to support the process changes The overall strategy to comparability assessment is appropriate.

Overall, based on the presented results, it is agreed that the material derived from the different processes can be regarded comparable. Thus, a bridge between material used from different processes in clinical studies was appropriately established.

Quality Attributes and Analytical Methods

A summary of the quality attribute criticality assignment rationale for the marstacimab active substance was presented. The results of the criticality assessment and justifications is reasonable.

Evolution of analytical method was described and does not give rise to questions.

In-Process Extractables and Leachables

A risk assessment was performed for all marstacimab active substance in-process contact materials. The results of the assessment show an overall low potential total daily intake (TDI) of the extractables compared to the permissible daily exposure or recommended dietary allowances. Overall, it is agreed that the potential leachables associated with each process contact component of the marstacimab active substance manufacturing process pose negligible risk to humans.

Upstream Process Development and Characterisation

A risk assessment was performed to identify important unit operations, process parameters, and material attributes that could affect the critical quality attributes (CQAs) of the active substance and/or could significantly affect process performance.

A qualified bioreactor model was used to test the impact of process parameters on quality attributes of the product. The DoE studies appear well designed and reasonable process parameters and sufficient and critical quality attributes were assessed.

The Applicant summarised the experimental ranges applied in the multivariate DoE and the resulting acceptable range and whether the process parameter is regarded critical or non-critical.

Overall, the upstream process development was appropriately performed according to ICH Q8/Q9, and no issues have been identified.

Downstream Process Development and Characterisation

Based on multivariate DoE, characterisation studies, and risk assessments, several CPPs were identified due to their impact on CQAs.

As applicable, based on characterisation studies, platform knowledge and risk assessments, reasonable critical process parameters were identified for all other downstream process steps. Overall, the downstream process development was appropriately performed according to ICH Q8/Q9, and no issues have been identified.

Control Strategy

The final control strategy was summarised in a table identifying every process parameter/in-process test, its criticality assignment, the characterised range in development studies, the target/control limit/observed range for process validation, the acceptable range/control limit for process validation and the respective justification for acceptable range/control limit for commercial manufacturing. Overall, the section on development of the control strategy was well addressed.

Characterisation

Analytical characterisation was performed with the material derived from the commercial active substance manufacturing. A panel of analytical methods was used to evaluate primary structure, post-translational modifications, charge and size heterogeneity, higher order structure, and biological activity of marstacimab... Thus, it is agreed that the presented characterization of the material in this section can be regarded representative of the material used during the development process and clinical studies.

Overall, the characterisation results demonstrate that marstacimab has the expected structure and target binding properties.

Impurities

Process-related impurities (residual DNA, HCP, cell culture derived impurities, protein A) were appropriately identified and characterised over the whole development process from manufacturing process. It was shown that impurity removal is consistent and will remove process-related impurities below the specified limits. This was also validated during the PPQ runs. Thus, it is agreed that expect for HCP no routine testing of process-related impurities is warranted.

It is agreed that routine in-process testing, and active substance release testing ensures control over potential contaminants and adventitious agents.

2.4.2.3. Specification

The specification for marstacimab active substance at release and during stability studies is provided and includes control of identity, purity and impurities, potency and other general tests. The acceptance criteria are applicable from batch release to end of shelf-life.

The specification is based on development experience with marstacimab, process characterisation and process validation data as well as data from active substance batches used in non-clinical and clinical studies. The specification is based on understanding of the control strategy to ensure that critical quality attributes (CQAs) are controlled to appropriate levels. In general, the strategy for justification of the specification is acceptable and the presented limits can be regarded acceptable.

Analytical Procedures

Compendial methods were appropriate established.

The non-compendial methods are described in sufficient detail. Used equipment, operating parameters, reagents and standards, buffers/solutions are listed. Furthermore, the sample preparation and procedure are described. The system suitability, assay and sample acceptance criteria are listed as well and found suitable to confirm that the methods are performing as expected during release testing. Were applicable, representative figures and results were presented. The Applicant confirmed that method validation is applicable on the facility where the AS testing is accomplished. Overall, the non-compendial analytical methods have been appropriately validated for their suitability for intended use according to ICH Q2(R1).

Reference Standard

For commercial manufacturing, the Applicant established a two-tiered reference standard system. The primary reference material (PRM) and the working reference material (WRM) are derived from the active substance (AS) by the commercial manufacturing process. . A bridging study was performed to ensure correct potency/biological activity assignment of the PRM against the previous clinical reference material (CRM). Thus, the traceability of potency values from clinical material to commercial material is appropriately established. Furthermore, an acceptable protocol for the preparation of future reference materials was provided.

Batch Analyses

Release results of all manufactured batches were provided and conformed to release criteria that were in place at the respective time. Overall, the results appear consistent. Comparability between process variants was appropriately established.

Container Closure

The container closure system used for the marstacimab active substance are ethylene vinyl acetate (EVA) bags.. The choice of the container/closure is justified and supported by pharmacopoeial compliance of the materials and stability data.

The bags are provided sterile by the manufacturer meeting the sterility assurance level of 10^{-6} according to ISO 11137. Overall, the container closure specification covers all expected attributes and is acceptable.

2.4.2.4. Stability

The Applicant is claiming a marstacimab active substance shelf life of 48 months when stored at the recommended temperature in EVA bags.

The shelf-life claim is based on the real-time, real-temperature data from the primary stability studies, therefore, can be regarded acceptable.

In addition, data from supportive stability batches at long term and accelerated conditions are provided..

The real-time stability data of the primary stability batches over 48 months at frozen condition show that all tested quality attributes conform to their clinical and commercial stability specification at all tested time-points. It is agreed that there are no apparent trends over time. Real-time stability data of supportive batches confirm the data established for primary stability batches.

The proposed shelf-life of 48 months stored at frozen conditionfor the active substance is acceptable.

2.4.3. Finished Medicinal Product – Prefilled Syringe

Description of the product and Pharmaceutical Development

Marstacimab finished product (FP) is provided at pH 5.8 in a strength of 150 mg/mL. The finished product is a colourless to light yellow solution supplied in a 1 mL glass (Type I) prefilled syringe. The finished product contains no preservative. Container closure system is adequately outlined. An overfill is included to (ensure that a 1 mL nominal volume can be delivered from the prefilled syringe. A successful confirmatory study was conducted looking at the delivery system hold-up (DSHU) and delivered volume of marstacimab in the syringe.

The formulations of marstacimab active substance and bulk finished product (prior to filling) are the same. The active substance is formulated in L-histidine, L-histidine monohydrochloride, sucrose, disodium edetate, polysorbate 80 and water for injections in the same excipient concentrations as in the finished product. There are no novel excipients used in the manufacture of marstacimab finished product are of human or animal origin. All excipients are compendial grade according to Ph. Eur.

The robustness of the marstacimab formulation was evaluated through multiple studies to assess the capability of the formulation to protect the drug against various stresses.

The physicochemical and biological properties relevant to the safety, efficacy, quality, or manufacturability of the finished product were investigated from early development through process validation (PV, also referred to as process performance qualification (PPQ)), using a range of analytical procedures.

The formulation was used throughout pre-clinical and clinical development varying only the concentration of marstacimab to enable subcutaneous administration and dose adjustments that occurred during clinical development. The experimentally measured levels of excipients tested in a robustness study showed that during commercial manufacturing, the release testing of pH and osmolality is sufficient to ensure the control of excipients. Submitted long-term and accelerated stability data provided evidence that the marstacimab finished product quality is robust to variations in excipient concentrations.

Manufacturing process development history and site changes are described with sufficient detail, the finished product lots used in each stage of development and the clinical studies provided. Manufacturing process development was performed extensively.

The process development and characterisation studies represent a combined experience derived both from laboratory scale studies using scale-down models as well as from full-scale studies and manufacturing conducted within the commercial production environment. Scale-down models to characterise the manufacturing process are sufficiently described in the Process Development and Characterisation Studies.

The choice of excipients (histidine, sucrose, disodium edetate, polysorbate 80, pH 5.8) have remained the same throughout development history of marstacimab including inclusion in the pivotal phase 3 clinical studies. Process development to support operations related to the drug product manufacture, from active substance thaw to filling and inspection were performed.

In addition, studies were also performed to support finished product storage and finished product shipping. Information about these studies were sufficient and results within these studies met the appropriate acceptance criteria.

Hold time studies were performed to establish hold times for marstacimab active substance and bulk finished product within the finished product manufacturing process in terms of physicochemical stability. The hold times are supported from a physicochemical stability perspective.

A risk-based approach as described in ICH Q9 Quality Risk Management was employed to guide the selection of process parameters to be investigated during process characterization studies.

Product attributes categorised as elemental impurities or extractables/leachables were evaluated in dedicated risk assessment/experimental programs.

QAs relevant to finished product and their classifications are presented and justified. Quality attributes (QAs) were assessed during development with methods that were intended to be used for commercial release and stability testing.

Criticality assessment of quality attributes is explained in detail.

Overall, the approach for identification of CQAs and the criticality assignment appears reasonable and sufficiently justified. The strategy for controlling of CQAs, relevant for the finished product, is deemed satisfactory.

The finished product consists of the marstacimab finished product within the container closure system (syringe barrel), a PFS plunger rod (non-product contact), and a PFS finger grip (back stop) (non-product contact). Primary packaging materials with contact to the finished product are of Ph. Eur. quality. No

substance of safety concern is leaking into the finished product as indicated by results of leachables and extractables testing.

A Notified Body Opinion for the PFS was submitted by the applicant, confirming full compliance with the relevant GSPRs.

Syringeability refers to the force required for the injection of a given solution at a given injection rate. The design and user requirements set for the marstacimab fully assembled PFS have been met.

Compatibility of marstacimab FP with its excipient and primary packaging materials has been shown in formulation studies and confirmed by stability data.

2.4.3.1. Manufacture of the product and process controls

All sites involved in manufacture, control and storage of the finished product operate in accordance with EU GMP.

The finished product manufacturing process consists of thawing of the active substance, followed by transfer to a manufacturing vessel to begin bulk finished product (FP) manufacturing. A formulation buffer is prepared and used to dilute the AS, in an optional one-step dilution, to the target protein concentration of 150 mg/mL.

The formulated bulk FP is then filtered through a bioburden reduction filter into a holding vessel and subsequently filtered through redundant sterile filters on the filling line and aseptically filled into syringes. After visual/ automatic inspection, the PFS are labelled and packaged and stored at a defined temperature range.

Maximum hold times of the finished product in-process materials are provided. These hold times are supported by data generated during process development and process validation.

Regarding reprocessing, a single bioburden reducing refiltration step of bulk product using a new 0.2 µm bioburden reducing filter is allowed in the event of technical failure. Repeated bioburden reducing filtration step is validated.

In-process hold times and time out of refrigeration (TOR) hold time is deemed acceptable, based on stability studies demonstrating that FP is stable under out-of-refrigeration conditions in excess of the time required for routine manufacturing operations.

Process validation was performed on three consecutive PPQ or PV lots

Validation data are submitted from active substance (AS) thawing, formulation of bulk finished product (pooling and dilution of pooled AS with buffer), bioburden filtration and re-filtration, sterile filtration, aseptic filling, and inspection of the FP syringes. Refreeze and rethaw and refiltration steps were adequately validated. Stability studies were performed, monitoring the effect of in-process hold times and cumulative hold times on the microbiological and physicochemical quality. Sterilisation methods of filter membranes and other product contact equipment, media filling process and shipping is also adequately validated. All validation results were within predefined acceptance criteria.

Based on the data provided the manufacturing process of marstacimab FP seems to be robust and provides a product that meets quality and stability attributes.

2.4.3.2. Product specification

Specification for the finished product in pre-filled syringe includes control of identity, purity and impurities, potency and other general tests.

Quality attributes are adequate, analytical procedures are well chosen and partly compendial. Acceptance criteria are based on data gained during development- and stability studies and are thoroughly justified.

Compendial analytical procedures were verified, non-compendial methods) were validated against reference material.

A summary of marstacimab finished product lots is provided, along with all the parameters tested within specifications.

Analytical procedures:

For all test methods SOPs and for the non-compendial assays for the FP, validation studies were performed in line with current compendial Ph. Eur. methods and ICH Q2(R1). Relevant validation parameters for each test method were taken into consideration. Test methods seem to be validated appropriately and can be accepted.

Furthermore, documents of the analytical method transfer exercises (AMTE), where appropriate, were submitted. Validation of Analytical Procedures, and the results from comparative testing are presented. All method system suitability/assay acceptance and transfer acceptance criteria were met. The results obtained by the receiving lab were within the performance of the analytical procedures and seems acceptable.

Batch analysis:

Batch analysis data from all Marstacimab finished product lots used for clinical trials, stability, and process validation are submitted. All parameters tested were within the defined specifications. The data submitted demonstrate consistency and conformity in the manufacturing process of Marstacimab finished product.

Characterisation of impurities:

An evaluation of the potential for N-nitrosamine impurity formation by review of process chemistry used to manufacture the active substance and finished product and the container closure system was conducted. No risk for small molecule nitrosamine (cohort of concern) formation was identified. From the toxicological perspective, there is no risk of the marstacimab molecule itself forming a nitrosamine requiring cohort of concern control. Sufficient information about the potential N-nitrosamines risk was submitted.

An elemental impurities risk assessment on marstacimab was performed according to ICH Q3D. The three process performance qualification finished product lots (PPQ) showed that all elements were below the control threshold and required no further assessment or control. Furthermore, the applicant states that no additional impurities arise from the finished product process. Therefore, the product related impurities in marstacimab finished product are the same as those found in the active substance.

2.4.3.3. Stability of the product

To support the shelf-life claim of 24 months at 2-8 °C and up to 7 days at 8-30 °C (within the 24-month shelf-life), Stability studies were performed in accordance with ICH guidelines.

A photostability study was performed according to ICH Q1B. The results demonstrated that the product is photolabile, but stable if stored in secondary packaging. This information has been included in SmPC.

The data provided supports the shelf-life claim of 24 months when stored at the recommended temperature of 2-8 °C and short-term storage between 8-30 °C for up to 7 days (within the 24-month shelf-life).

2.4.4. Finished Medicinal Product - Prefilled Pen

2.4.4.1. Description of the product and Pharmaceutical Development

The prefilled pen (PFP) is a single-dose, disposable pen that encloses a 1 mL long Type I glass prefilled syringe as described in 3.2.P Prefilled Syringe sections. Together they form a single integral product, intended exclusively for use in the given combination. The final assembled pen consists of a prefilled syringe, a syringe clip and two subassemblies (power pack and front assembly).

The description and composition of the PFP presentation and container closure system is adequately described.

The applicant has provided a comprehensive overview of the pharmaceutical development of the medicinal product combined with an integral medical device and has included a Notified Body Opinion confirming full compliance with the relevant GSPRs. The assembly of the pen is an automated process.

The applicant defined the quality target profile (QTPP) for the Prefilled Pen. The Prefilled Pen assembly process is adequately described.

The design verification was adequate and demonstrated to be compliant with ISO 11608. Critical quality attributes were defined for attributes that directly relate to usability and the safety of the user and will be routinely tested as part of release and stability.

Human factors testing on participants representative of the intended marstacimab pen user population included iterative evaluations of the marstacimab user interface, including the pen and label, the instructions for use with and without training. . The prefilled pen was validated to be safe and effective when used by the intended users in the intended use environment.

A risk analysis was performed using FMEA (failure mode effect analysis). The overall residual risk associated with the product has been reduced as far as possible and is acceptable when balanced against the benefit of its intended use, which is supported.

2.4.4.2. Manufacture of the product and process controls

Appropriate evidence of GMP compliance of the site responsible for pen manufacture has been provided.

Each prefilled pen lot can be manufactured using a single lot of prefilled syringes. The manufacturing process is adequately described in the dossier and in-process tests are considered sufficient.

The Process validation was performed. It consisted of in-process controls and release tests at the end of manufacture.

A shipping validation was performed to assess all possible conditions that are expected to arise during the shipping process. The validation demonstrated that the pen is not impacted by the shipping hazard conditions that could occur during the transportation process.

Overall, the manufacturing process was adequately described and validated.

2.4.4.3. Product specification

The release and stability specification for the marstacimab 150 mg/mL pen is provided.

Analytical methods are described, and the methods appear to be appropriately validated. Adequate method validation was performed.

Batch analysis was performed on clinical, stability and process validation material. All lots were within predefined acceptance criteria.

The specification limits were justified based on lot release, process validation and stability testing and considered acceptable.

The sample numbers for release and post-stability testing are calculated using binomial principles based on acceptable risk-based quality limits, which is supported. In summary, the set of quality attributes tested is acceptable.

The section on the container closure system is considered to be sufficient and no questions are raised.

2.4.4.4. Stability of the product

The Applicant has performed several stability studies including long-term, accelerated, time out of refrigeration, thermal stress, and thermal cycling.

It is accepted that for the assembled pen, the stability studies only focus on appearance and functionality parameters since the marstacimab finished product is not in contact with the device. Results were within acceptance criteria.

The 24 months shelf-life claim for the prefilled pen (at recommended storage conditions of 2-8 °C with a maximum of 30 °C for a single period of up to 7 days within the shelf-life), is sufficiently justified with provided long-term stability data.

The Applicant has provided a commitment to perform post-approval annual stability studies.

2.4.4.5. Adventitious agents

Multiple measures are implemented to ensure product safety with regards to non-viral and viral adventitious agents. The measures include evaluation and testing of raw material, testing of cell banks and process intermediates for microbial and viral contaminants, testing of microbial attributes as in-process controls and release. Implementation and validation of virus clearance steps and steps contributing to virus reduction.

Non-viral adventitious agents

MCB, WCB and end-of-production cell bank (EOPCB) were tested for the absence of bacterial, fungal and mycoplasma contamination according to Ph. Eur. 2.6.1 and 2.6.7 at appropriate steps of manufacture. Tests

for bioburden, mycoplasma and endotoxin are performed at multiple steps during the manufacturing process for active substance and finished product. No animal-derived materials were used in MCB and WCB manufacture or during active substance and finished product manufacturing. During establishment of the parental CHO cell line, cells were exposed to animal derived components (i.e. FBS) and the Applicant referred to valid certificates of suitability issued by the EDQM.

In conclusion, the risk for microbial contamination is adequately controlled and the risk with regard to TSE is minimal.

Adventitious viruses

Cell banks were tested with various assays. Unprocessed bulk harvest was tested for the absence of adventitious viruses

In conclusion, testing of cell banks and unprocessed bulk was performed according to guideline ICH Q5A. No adventitious viruses were detected except for A-type particles.

Virus clearance studies

The virus clearance capacity of the manufacturing process was assessed with virus clearance studies using small scale models of the respective large-scale manufacturing process steps. The design of the studies appears to be in line with guideline ICH Q5A. Tabular comparison of the process parameters for the manufacturing scale and the small-scale process steps were provided. Details on small scale models are adequately described.

A number of process steps were evaluated using a selected panel of viruses that represents a broad range of virus types with different physicochemical characteristics. It is agreed that the chosen viruses represent relevant models that may possibly contaminate the active substance.

The total process clearance determined by summation of removal/inactivation methods implies an acceptable safety margin regarding retrovirus-like particles.

In conclusion, the inactivation/clearance steps provide for an effective and robust overall clearance capacity for adventitious viruses. The risk of potential contamination and transmission of bacterial, viral or TSE agents appears to be acceptably low.

2.4.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

An extensive and well organised Module 3 of overall good quality for Hympavzi was provided by the Applicant. The product is a monoclonal IgG1 antibody that binds and neutralises tissue factor pathway inhibitor (TFPI) to enhance the extrinsic pathway and reduce or eliminate the need for replacement of coagulation factors FVIII or FIX. Appropriate confirmation of GMP compliance of the active substance and finished product manufacturing and testing sites was shown. The product is indicated for children > 12 years of age, therefore paediatric aspects related to formulation and the presentations provided are not of concern.

Active substance

The marstacimab active substance manufacturing process and control strategy was described in detail. Process parameters (CPP and non-CPPs), CMA and in-process tests and their respective acceptance ranges

are presented for every manufacturing process step. Sufficient detail on raw and starting materials including information on quality and control of these materials is provided.

The active substance is manufactured in a bioreactor. The purification process provides two dedicated virus reduction steps in combination with chromatography steps. Virus clearance studies were performed at small-scale. Overall, an effective and robust clearance capacity for enveloped and non-enveloped adventitious viruses was confirmed. The risk of potential contamination and transmission of bacterial, viral, or TSE agents appears acceptably low.

The active substance specification is acceptable.

Process validation of the intended commercial upstream and downstream active substance manufacturing was appropriately performed. Impurity clearance, hold times, resin and membrane lifetime, reprocessing and shipping were also validated either at small-scale and/or commercial scale.

Process development for selected manufacturing steps was performed in qualified small-scale models.

Process parameters with expected influence on CQAs were studied using DoE studies. Overall, the process was appropriately developed. Comparability between the process variants was appropriately established. The material used in (pre-)clinical studies can be regarded representative of the commercial scale material.

The active substance was characterised with an extensive set of analytical methods.

The layout for the control of AS is generally approvable. The selection of analytical techniques is considered adequate. Detailed method descriptions have been provided. Validation of the methods is considered acceptable. An adequate two-tiered reference standard system has been established.

The description of the Container Closure System is considered acceptable.

The shelf-life claim of 48 months at -20°C for marstacimab AS is approvable as the shelf-life claim is supported by the submitted stability study results.

Finished product (Syringe)

The presentation and content of the dossier of FP (syringe) is satisfactory. Marstacimab finished product (FP) is provided at pH 5.8 in a strength of 150 mg/mL. The finished product is a colourless to light yellow solution supplied in a 1 mL single-dose glass (Type I) prefilled syringe. The finished product contains no preservative and is for single-dose only. An overview of formulation development is provided supporting the proposed composition.

The FP of marstacimab is well characterised. The finished product is manufactured with a validated process and satisfactorily controlled to ensure consistent quality. Quality attributes chosen for release and stability specification are approvable, the choice of analytical procedures as well. An elemental impurities risk assessment on marstacimab was performed according to ICH Q3D. Results showed that all elements were below the control threshold and required no further assessment or control routinely for finished product release by the company. An appropriate N-nitrosamines risk assessment was submitted confirming no risk for nitrosamine formation.

The container closure system has been adequately described and appears to be suitable for the intended use. The Applicant has provided a comprehensive overview of the pharmaceutical development of the medicinal product combined with an integral medical device and has included a Notified Body Opinion.

Many stability studies with different conditions were performed by the company. The Applicant is claiming a marstacimab finished product shelf life of 24 months when stored at the recommended temperature of 2-8

°C. Additionally it is proposed that marstacimab finished product can undergo short term storage between 8-30°C for up to 7 days (within the 24 months shelf life). The proposed shelf life is acceptable.

All raised other concerns were appropriately addressed.

Finished product (Prefilled Pen)

The prefilled pen is a single-dose, disposable pen that encloses a prefilled syringe. Together they form a single integral product, intended exclusively for use in the given combination. The final assembled pen consists of a prefilled syringe, a syringe clip and two subassemblies (power pack and front assembly). The provided information in the finished product section for the prefilled pen is satisfactory. Notified body opinion on the prefilled pen as a device has been submitted. Description and composition of the Finished product has been sufficiently described. Details on the individual components and functions of the prefilled pen are provided. The pharmaceutical development section provides an overview of the manufacturing process development including a process characterization study.

A design verification study demonstrated compliance with ISO 11608 and the product validation included a human factors testing, validating the pen to be safe and effective when used by the intended users in the intended use environment.

The pen manufacturing process consists of pen assembly, labelling and packaging. A flow chart and a brief summary of the IPCs is provided. The process and shipping validation are sufficiently described.

The control strategy of the prefilled pen appears appropriate, and the proposed release and stability specifications are acceptable. Analytical methods used for release and stability have been sufficiently described. Analytical methods appear appropriately validated.

The container closure system has been adequately described and appears to be suitable for the intended use.

Based on the provided stability data, the proposed shelf-life of 24 months when stored at 5 ± 3 °C with storage at a maximum of 30 °C for a single period of up to 7 days is considered acceptable. A commitment to perform post-approval annual stability studies is provided.

All raised concerns were appropriately addressed.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Hympavzi is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

No further recommendations for future quality development have been made.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Hympavzi is approvable from the quality point of view.

2.5. Non-clinical aspects

2.5.1. Introduction

Marstacimab (PF-06741086) is a human mAb that binds to and inhibits the activity of TFPI, an endogenous inhibitor of coagulation. TFPI is a Kunitz-type protease inhibitor that negatively regulates thrombin generation within the extrinsic pathway of coagulation by rapidly inactivating the protease functions of FXa and the Factor VIIa/Tissue Factor (FXa/FVIIa/TF) complex (Baugh *et al*, 1998; Girard *et al*, 1989). TFPI initially binds to and inhibits the FXa active site via its second Kunitz inhibitor domain (K2). This complex then binds to and inhibits the Factor VIIa active site through its first Kunitz inhibitor domain (K1) to form a quaternary complex with full inhibitory activity (Broze & Girard, 2012). In haemophilia, the production of FXa and thrombin via the extrinsic pathway is insufficient to overcome the intrinsic pathway deficiencies of FVIII (haemophilia A) or Factor IX (haemophilia B), due to the tight negative regulation of the pathway by TFPI. Neutralising the activity of TFPI may serve to enhance the extrinsic pathway and bypass deficiencies in the intrinsic pathway of coagulation.

The nonclinical PK strategy supported the nonclinical pharmacology and nonclinical safety evaluation of marstacimab. Single-and repeat-dose PK were characterised following SC or IV dosing of marstacimab in Wistar Han rats and *Cynomolgus* monkeys. Repeat-dose PK were also characterised after dosing of marstacimab co-administered with NovoSevenRT, or FEIBA, or Byclot. Validated ligand binding assays were used to support the TK and ADA evaluations in repeat-dose GLP toxicity and TK studies in Wistar Han rats (up to 6 months) and *Cynomolgus* monkeys (up to 3 months). The toxicity of marstacimab was evaluated in Wistar Han rats and *Cynomolgus* monkeys in GLP-compliant repeat-dose studies of up to 3 months (monkeys) or 6 months (rats) in duration. A fertility and early embryonic toxicity study in male rats and a single-dose SC local tolerance study in rats were also conducted. Doses in these studies were administered by SC and/or IV injection since they were the routes of administration used during clinical development. The nonclinical toxicity program for marstacimab also included a GLP-compliant TCR study, and non-GLP *in vitro* human C1q and FcγR binding assays and a CRA.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Pharmacological activity of marstacimab was assessed in nine *in vitro* studies, investigating binding of marstacimab to its target, the Tissue Factor Pathway Inhibitor (TFPI), and its functional activity, inhibition of TFPI and therefore neutralisation of TFPI activity, resulting in promotion of the TF/FVIIa extrinsic pathway of the coagulation cascade.

Two *in vitro* binding studies were conducted with marstacimab to confirm binding to the K2 domain of Tissue Factor Pathway Inhibitor (TFPI). In study PF-06741086_28APR15_072904, binding affinity and kinetics of marstacimab to human, mouse, rat, rabbit and *Cynomolgus* monkey TFPI K1K2 was investigated by Surface Plasmon Resonance (SPR), whereas in study PF-06741086_14Nov22_121926, the same technique was used to confirm binding of marstacimab to human TFPI K1K2 and TFPI K1 and non-binding to TFPI K1. SPR analysis in study PF-06741086_28APR15_072904 revealed low dissociation constant (KD) values of marstacimab for human ($3.7 \text{ nM} \pm 0.28$), mouse ($0.575 \text{ nM} \pm 0.05$), rat ($1.57 \text{ nM} \pm 0.04$), rabbit ($4.25 \text{ nM} \pm 0.05$) and *Cynomolgus* monkey ($1.22 \text{ nM} \pm 0.03$) TFPI K1K2 within the nanomolar or even sub-nanomolar

range. Binding kinetics of marstacimab to human and rabbit TFPI K1K2 were most similar, when compared to the other species. The lack of binding to TFPI K1 could be confirmed in study PF-06741086_14Nov22_121926, where a KD of $2.63 \text{ nM} \pm 0.08$ to TFPI K2 and a KD of $7.91 \text{ nM} \pm 0.33$ to combined TFPI K1K2 domains was achieved. The almost three-fold higher dissociation constant of the combined domains TFPI K1K2 compared to the single TFPI domain K2 was discussed by the Applicant and explained by the higher (slower) on-rates (k_a) of TFPI K1K2, maybe due to its larger size.

Two enzymatic chromogenic-based assays (study PF-06741086_06APR15_085202), the FXa Inhibition Reversal Assay and the TF-FVIIa-FX Inhibition Reversal Assay, were conducted to verify inhibition of TFPI by marstacimab (0-80000 ng/mL and 0-32000 ng/mL, respectively) and the resulting increase in Factor Xa activity. In both assays of study PF-06741086_06APR15_085202, a dose-dependent response was observed by marstacimab, with estimated EC50 values of 1312 ng/mL (8.75 nM) in the FXa Inhibition Reversal Assay and 1985 ng/mL (13.23 nM) in the TF-FVIIa-FX Inhibition Reversal Assay.

Thromboelastography (TEG) was used to examine the effect of marstacimab [up to 32 $\mu\text{g}/\text{mL}$ (213.3 nM) in donor 2 and 3, up to 16 $\mu\text{g}/\text{mL}$ (106.7 nM) in donor 1 blood] on clot formation dynamics (as speed and strength determined by the clotting/reaction time (R), clot formation time/clot firmness (K), alpha angle and maximum amplitude) in non-haemophilic human whole blood of three different donors (study PF-06741086_01Apr15_142056). TEG analysis of non-haemophilic human whole blood of all 3 donors revealed dose-dependent decreases in clotting time (R) and clot formation time (K), no changes in maximum amplitude and an increase in alpha angle, with increasing concentrations of marstacimab. It is to note, that a high donor-to-donor variability was observed.

In study PF-06741086_07APR15_123404, three haemostatic assays were performed to investigate the inhibitory activity of marstacimab on TFPI in non-haemophilic human plasma of healthy volunteers, the activated partial thromboplastin time (aPTT) assay, which targets on the intrinsic pathway of the coagulation cascade, the dilute prothrombin time (dPT) assay targeting the extrinsic pathway and the thrombin generation assay (TGA). Marstacimab was used in concentrations ranging from 0.8 to 56000 ng/mL (373.3 nM) in the aPTT and dPT assay and from 1.6 ng/mL to 16000 ng/mL in the TGA assay. The dPT assay was conducted as well in non-haemophilic rabbit and *Cynomolgus* monkey plasma, using similar or the same concentrations of marstacimab, respectively. As expected, no effect on the aPTT clotting time was observed, whereas in contrast, a dose-dependent shortening of the dPT clotting time was seen in the dPT assay in non-haemophilic human, rabbit and *Cynomolgus* monkey plasma, with EC50 values of 406 ng/mL (2.7 nM), 629 ng/mL (4.2 nM) and 273 ng/mL (1.7 nM), respectively. In the TGA assay, thrombin generation increased with increasing doses of marstacimab in non-haemophilic human plasma, accompanied by several changes in the quantitative parameters of the TGA assay (e.g. increase in velocity index and decrease in lag time).

Study PF-06741086_07APR15_135025 describes the influence of marstacimab on coagulation in the presence of haemophilic plasma, as this reflects the condition of disease. Therefore, an aPTT, a dPT and a TGA assay were performed using the plasma of four severe haemophilia A patients, one severe haemophilia A patient with inhibitor (BU=176) and one severe haemophilia B patient (all below 1% Factor VIII or IX activity, respectively).

Marstacimab was used at concentrations ranging from:

- 0.8 ng/mL (0.0053 nM) to 56000 ng/mL (373.3 nM)] in the aPTT and dPT assay
- 0.16 $\mu\text{g}/\text{mL}$ (1.07 nM) to 80 $\mu\text{g}/\text{mL}$ (533.3 nM) were applied in the TGA assay.

- 20 to 0.0002 µg/mL when FVIIa was added to plasma of one haemophilia A donor in concentrations ranging, marstacimab was added at a final concentration of 16 µg/mL (106.7 nM) and a TGA was conducted again.

Unexpectedly, slight decreases in aPTT clotting times were observed in all haemophilic plasmas at the three highest concentrations of marstacimab (56000 ng/mL, 16000 ng/mL and 8000 ng/mL) but were obviously far from the normal range of non-haemophilic, normal plasma. As observed in non-haemophilic human plasma (study 123404), dose-dependent shortening of the dPT clotting time was seen in all haemophilic plasmas as well, with similar EC values ranging from 380.5 to 471.4 ng/mL (2.3 to 3.1 nM). The thrombin generation assay revealed dose-dependent increases in thrombin generation with increasing doses of marstacimab in all haemophilic plasma samples. The presence of increasing doses of rFVIIa, without marstacimab, led to a dose-dependent increase in thrombin generation. Addition of marstacimab further increased thrombin generation, even to normal plasma levels or above and showed to be dose-dependent at lower rFVIIa concentrations (up to 0.02µg/ml).

In study PF-06741086_31Mar16_122443, the effect of marstacimab on thrombin generation with and without the combination of rFVIIa (NovoSevenRT, eptacog alfa) was investigated in haemophilic plasma (from 6 haemophilia A donors, 3 haemophilia A donors with an inhibitor and one haemophilia B donor) by a thrombin generation assay. Following samples were analysed: vehicle-treated haemophilic plasma; 2µg/mL rFVIIa-treated haemophilic plasma; 0.5, 1, 2, 4, 8 or 16µg/mL marstacimab-treated haemophilic plasma; 0.5, 1, 2, 4, 8 or 16µg/mL marstacimab-treated haemophilic plasma in addition of 2µg/mL rFVIIa; untreated non-haemophilic plasma and non-haemophilic plasma dosed with 16 µg/mL marstacimab. Increasing doses of marstacimab at 0.5, 1, 2, 4, 8 and 16µg/mL to haemophilic plasma increased peak thrombin levels and decreased lag time, when compared to vehicle control. Addition of rFVIIa at 2µg/mL to marstacimab at 0.5, 1, 2, 4 and 8µg/mL in haemophilic plasma led to similar peak thrombin levels as seen with marstacimab alone, whereas a slight additive effect of rFVIIa at 2µg/mL and marstacimab at 16µg/mL was observed after co-treatment. Overall, in haemophilic plasma, marstacimab at 16µg/mL with and without co-treatment of 2µg/mL rFVIIa reached comparable peak thrombin levels as observed in untreated non-haemophilic plasma. Addition of 16µg/mL marstacimab to non-haemophilic plasma led to the highest increase in thrombin generation. Summary of observed peak thrombin levels: (1) vehicle control: 26-76nM in Haemophilia A, 24-66nM in Haemophilia A with Inhibitor, 81nM in Haemophilia B; (2) rFVIIa at 2µg/mL: 45-113nM in Haemophilia A, 46-89nM in Haemophilia A with Inhibitor, 131nM in Haemophilia B; (3) marstacimab at 16µg/mL: 82-172nM in Haemophilia A, 88-166nM in Haemophilia A with Inhibitor, 174nM in Haemophilia B; (4) marstacimab at 16µg/mL and rFVIIa at 2µg/mL: 102-178nM in Haemophilia A, 99-157nM in Haemophilia A with Inhibitor, 167nM in Haemophilia B; (5) untreated non-haemophilic plasma: 128-143nM; (6) non-haemophilic plasma treated with marstacimab at 16µg/mL: 171-198nM.

A thrombin generation assay was performed in study PF-06741086_26Jul18_045123 to evaluate individual and combined treatment of plasma derived activated prothrombin complex concentrate (aPCC; FEIBA) and marstacimab in haemophilic inhibitor plasmas (from four haemophilia A donors and one Factor IX immune-depleted plasma with the addition of an inhibitory antibody as haemophilia B plasma). For individual treatments, aPCC was dosed at 0.063, 0.125, 0.5 or 1 U/mL and marstacimab at 0.5, 1, 2, 4, 8, or 16 µg/mL, whereas the highest dose of 1 U/mL aPCC or 16µg/mL marstacimab was used in combination with increasing doses of marstacimab or aPCC, respectively. Human non-haemophilic plasma with and without addition of marstacimab at 16µg/mL was used for comparison. Peak thrombin values increased dose-dependently in haemophilic plasmas with increasing doses of either aPCC or marstacimab, the latter indicating to reach a plateau at >0.5µg/mL marstacimab. After addition of 1 U/mL aPCC to increasing doses of marstacimab in haemophilic plasma, an additional increase in thrombin generation was observed, reaching

a plateau at marstacimab $>0.5\mu\text{g}/\text{mL}$. Addition of $16\mu\text{g}/\text{mL}$ marstacimab to increasing doses of aPCC led to a dose-dependent increase in peak thrombin values. Focusing on a combined treatment with aPCC at $1\text{ U}/\text{mL}$ and $16\mu\text{g}/\text{mL}$ marstacimab, each expected plasma levels which could be achieved after clinical administration, the latter corresponding to a C_{max} following a single SC dose of 300mg marstacimab, an additive increase in peak thrombin generation, but no additive decrease in lag time were observed, whereas each single treatment led to an increase in peak thrombin and decrease in lag time itself. Reported values for peak thrombin: (1) untreated haemophilic inhibitor plasma A (HA): $14.6\text{--}19.05\text{nM}$, untreated haemophilic inhibitor plasma B (HB): 30.51nM ; (2) untreated non-haemophilic plasma: $89.62\text{--}135.23\text{nM}$; (3) HA treated with $1\text{ U}/\text{mL}$ aPCC: $74.73\text{--}110.08\text{nM}$, HB treated with $1\text{ U}/\text{mL}$ aPCC: 163.08nM ; (4) non-haemophilic plasma with $16\mu\text{g}/\text{mL}$ marstacimab: $160.43\text{--}256.73\text{nM}$; (5) HA with $16\mu\text{g}/\text{mL}$ marstacimab: $72.92\text{--}109.69\text{nM}$, HB with $16\mu\text{g}/\text{mL}$ marstacimab: 70.14nM ; (6) HA with combined treatment of $1\text{ U}/\text{mL}$ aPCC and $16\mu\text{g}/\text{mL}$ marstacimab: $209.26\text{--}240.57\text{nM}$, HA with combined treatment of $1\text{ U}/\text{mL}$ aPCC and $16\mu\text{g}/\text{mL}$ marstacimab: 254.11nM .

Study PF-06741086_14Oct22_103228 investigated combined treatment of Byclot at concentrations of FVIIa/FX at $2/20$, $1/10$, $0.5/5\text{ }\mu\text{g}/\text{mL}$ and marstacimab at $16\mu\text{g}/\text{mL}$ in haemophilia A and haemophilia B plasma with inhibitor (for the latter, haemophilia B plasma was spiked with a FIX inhibitory monoclonal antibody) by a thrombin generation assay. Non-haemophilic plasma and haemophilia A and B plasma with inhibitor, each with and without $16\mu\text{g}/\text{mL}$ marstacimab, were used as controls for comparison. Furthermore, the dose-response relationship of increasing doses of Byclot ($0.25/2.5\mu\text{g}/\text{mL}$ to $8/80\mu\text{g}/\text{mL}$) was examined in haemophilia A and B plasma with inhibitor. A dose-response relationship for Byclot at all concentrations tested was observed in haemophilia A and B plasma with inhibitor and mirrored by increases in peak thrombin (peak thrombin values ranging dose-dependently from 42.79 to 260.99 nM and 25.65 to 209.12 nM , respectively), ETP and VelIndex. Byclot led to a similar shortening of lag time at all concentrations in both, haemophilia A and B plasmas with inhibitor (decrease from 4.17min in untreated haemophilic plasma to Non-clinical evidence identifies marstacimab's mechanism of action in the well-defined extrinsic coagulation pathway: The two major coagulation pathways (intrinsic and extrinsic pathways) both ultimately lead to activation of Factor H, which in turn leads to thrombin generation. FVIII and FIX form a single enzymatic complex and thus deficiency of either component, in patients with haemophilia A and B, respectively, manifests in similar coagulation deficits. In in vitro spike-in assays, marstacimab similarly promoted haemostasis in haemophilic plasma from haemophilia A, B, and haemophilia inhibitor plasma in haemostatic assays, including TGA.

15.20nM and 6.15nM , respectively; lag time of 4.17min and 5.50min , respectively; non-haemophilic plasma: peak thrombin of 99.13 and 91.36 nM , lag time of 4.50min). A dose-dependent increase in thrombin generation was observed as well for the combined treatment of Byclot ($2/20$, $1/10$, $0.5/5\text{ }\mu\text{g}/\text{mL}$) and marstacimab ($16\mu\text{g}/\text{mL}$) in haemophilia A and B plasma with inhibitor, which showed an additive effect in peak thrombin (ranging from 209.85 to 291.22 nM in HA and from 156.22 to 228.61 nM in HB). A decrease in lag time with the combined treatment in haemophilia A and B plasma with inhibitor was observed (ranging from 1.83min to 2min and 2.17min to 2.33min , respectively).

Pharmacological activity of marstacimab was assessed in six ***in vivo* studies** conducted in male *Cynomolgus* monkeys, male haemophilia A and B mice or male Wistar Han rats.

Study 8299672 was conducted to investigate pharmacokinetics and pharmacodynamics of marstacimab in male *Cynomolgus* monkeys. Therefore, the animals (2/group) received either intravenous (IV) marstacimab at $1\text{mg}/\text{kg}$, $3\text{mg}/\text{kg}$ and $1\text{mg}/\text{kg}$ on day 1, day 8 and day 22, respectively (group 1), or IV marstacimab at $10\text{mg}/\text{kg}$ on day 1 and at $3\text{mg}/\text{kg}$ on day 22 but subcutaneous (SC) marstacimab at $10\text{mg}/\text{kg}$ on day 8 (group 2), or IV marstacimab at $1\text{mg}/\text{kg}$, at day 1 and day 22 but SC marstacimab at $3\text{mg}/\text{kg}$ on day 8 (group 3). Plasma concentrations for marstacimab and for total TFPI (by LC-MS) were determined pre and post dose [day 1: pre-dose, and at 0.083 , 6 , 24 , 48 , 72 , 96 , 120 , 144 , and 168 (just prior to the next dose)

hours post-dose; day 8: 0.083, 6, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312 (just prior to the next dose) and 336 hours post-dose; day 22: 0.083 hours post-dose] and a dilute prothrombin time assay (dPT) was conducted pre-and post-dose at various time points for group 1 at 1mg/kg IV marstacimab on day 1, for group 2 at 10mg/kg SC marstacimab on day 8 and group 3 at 3mg/kg SC marstacimab on day 8. A dose dependent increase in marstacimab plasma concentrations was observed. Mean C_{max} (20400, 54600 and 289000ng/mL), AUC_{168} (386000, 1950000 and 14100000ng*hrs/mL) and $t_{1/2}$ (12.3, 35 and 118 hours) increased with increasing doses of IV marstacimab at 1, 3 and 10mg/kg/dose, respectively. After SC administration of marstacimab at 3 and 10mg/kg/dose, an increase in mean C_{max} (18500 and 148000ng/mL, respectively), AUC_{336} (2360000 and 28200000 ng*hrs/mL, respectively) and $t_{1/2}$ (36.5 and 163 hours, respectively) was observed as well. Systemic plasma clearance (CL, in mL/min/kg) decreased with increasing doses after IV marstacimab administration. Furthermore, increases in marstacimab plasma concentrations correlated with increases in total TFPI concentrations in plasma and the other way round, total TFPI decreased with elimination of marstacimab. The dPT assay revealed a decrease in dPT clotting time after IV or SC administration of marstacimab at the respective doses tested in all groups, compared to baseline pre-dose values. At 3 mg/kg SC marstacimab, dPT clotting time decreased gradually up to 24 hours and then remained stable up to approximately 240 hours. In intravenously dosed animals at 1mg/kg marstacimab a more rapid decrease in dPT clotting time was noticed at 5 minutes post-dose, but with dPT values returning to baseline values approximately after 72-96 hours. At 10mg/kg SC marstacimab, mean baseline pre-dose values for both animals tested (animal 102447:107.7s and animal 102448: 106.8s) decreased as well, measured at 0.083, 24, 192 and 336 hours post dose (animal 102447: 90.8, 92.7, 91.1 and 92.5s, respectively and animal 102448: 88.5, 92.0, 90.1 and 89.9s, respectively).

In study PF-06741086_07APR15_135244, male haemophilia A and B mice (5 animals/group) were used as acute tail clip injury model and the duration of marstacimab's efficacy in the reduction of tail bleeding after injury at certain time points (0.5 hours in HB; 0.5, 24, 96, 189 and 240 hours in HA mice) postdosing intravenous marstacimab (6 mg/kg) or vehicle was assessed. Dose-response on tail bleeding obtained with increasing IV doses of marstacimab (0.5, 1, 2 or 6 mg/kg) administered to haemophilia A mice was investigated after 0.5 hours. Blood was collected for 10 minutes after tail clip, then blood volume as well as haemoglobin content, which was then converted to total blood loss (μ L), were determined for each mouse. Additionally, male haemophilia A and non-haemophilic WT C57BL6/J mice were used in the laser induced injury model using intravital microscopy imaging, detecting platelet accumulation and fibrin deposition with fluorescent labelled antibodies to platelet CD42c (Dylight 649) and fibrin (Alexa 488). Haemophilia A mice were intravenously dosed with 6 mg/kg of marstacimab, PBS saline (as negative control) or 200 IU/kg of rFVIII (as positive control) and 0.5 hours post-dose the cremaster arteriolar endothelium of the mice was injured by laser (7 to 12 injuries/mouse, 3 mice/group). Non-haemophilic WT C57BL6/J mice received saline before injury and served as control. Blood loss after tail clip injury showed to decrease dose-dependently with increasing doses of marstacimab in haemophilia A mice. At 0.5, 1, 2 or 6 mg/kg a decrease of 6.1%, 51%, 63.2% and 77.7% in bleeding was observed in haemophilia A mice. In haemophilia B mice, a decrease of 74% was noticed at 6 mg/kg marstacimab. Furthermore, a high reduction in blood loss was observed at 0.5 hours, which finally returned to baseline and control values after 240 hours in haemophilia A mice treated with 6mg/kg marstacimab (e.g. 77.9% reduction at 0.5 hours, 27.3% reduction at 189 hours). The laser induced injury model revealed a similar increase in platelet accumulation and fibrin deposition for haemophilia A mice treated with 6 mg/kg marstacimab or 200 IU/kg rFVIII but were far from the maximal level observed in non-haemophilic control animals. The haemostatic effect of marstacimab persisted to 168 hours.

In study number PF-06741086_31Mar16_121321, the effect of marstacimab on bleeding was investigated in haemophilic mice by using acute tail clip injury or laser-induced injury to provoke active bleed. Therefore, haemophilia B mice (5 mice/group) were intravenously treated with marstacimab at 6 mg/kg or vehicle and the volume of blood loss and haemoglobin content were determined 0.5 (marstacimab group and vehicle control), 72 and 192 (marstacimab groups only) hours post-dose, when bleeding was induced by tail clip. Haemophilic A mice received either IV marstacimab at 6 mg/kg (n=10), vehicle (n=11), or recombinant FVIII at 200 U/mg (n=5) immediately after tail clip or marstacimab at 1, 3 and 6 mg/kg (n=11, n=6 and n=8, respectively), recombinant FVIII at 200 U/mg (n=8) or vehicle (n=14) two minutes after bleeding onset caused by tail clip. In the laser-induced injury model, bleeding was investigated by intravital microscopy imaging in haemophilia A mice (n=18), where each mouse was injured twice, at first without and then with intravenous administration of marstacimab (at 6 mg/kg), immediately given after injury. In haemophilia B mice, a significant reduction of blood loss (65%) was observed at 0.5 hours post-dose marstacimab (6mg/kg) and to a less extend at 72 hours post-dose. In haemophilia A mice, immediate infusion of marstacimab (6mg/kg) or recombinant FVIII led to a decrease in blood loss of 60% or 84%, respectively. A dose-dependent reduction was observed due to IV administration two minutes after bleeding onset of 1, 3 (51%) and 6 mg/kg (76%) marstacimab. An increase in platelet accumulation (1.8-fold) and fibrin deposition (6-fold), analysed by area under the curve after laser injury in haemophilia A mice, was observed, when compared to untreated mice.

A non-GLP 10-day intravenous repeat dose administration study, number 16MA086, was conducted in male Wistar Han rats to investigate potential additive effects of a combined treatment of marstacimab at 50 mg/kg once daily on Days 1 and 8 and NovoSeven RT (eptacog alfa, activated), a blood coagulation factor VIIa (FVIIa), at 3 mg/kg once daily (QD) or 0.8 mg/kg (0.4 mg/kg twice daily (BID)) on day 8, 9 and 10. Marstacimab (at 50 mg/kg QD on Days 1 and 8) and NovoSeven RT (0.4, 1, or 3 mg/kg (QD) or 0.8 mg/kg (0.4 mg/kg BID) on Days 8-10) were also administered alone. Only combined once daily administrations of marstacimab at 50 mg/kg QD (Days 1 and 8) and NovoSeven RT at 3 mg/kg indicated an enhanced effect, reflected microscopically by an increased incidence and /or severity of minimal to mild, acute thrombi/emboli in the lung and injection site (tail). Treatment with Novoseven RT resulted in non-dose-related lower group means for PT, which were not changed by concomitant administration of marstacimab. Combined treatment of marstacimab and NovoSeven RT at 0.4 mg/kg BID led to slightly higher glucose values (1.17x-1.28x respective vehicle control group mean). Co-administration of marstacimab (50mg/kg QD) and NovoSeven RT (3mg QD or 0.4mg BID) did not alter systemic exposure, reflected by similar Cmax and AUC_t values when dosed alone. After dosing with NovoSeven RT, a delay in Tmax was noticed. For marstacimab (50 mg/kg), marstacimab (50 mg/kg)/NovoSeven RT (3 mg/kg), and marstacimab (50 mg/kg)/NovoSeven RT (0.8 [0.4 BID] mg/kg) at Day 8 following values data were reported, respectively: C_{max}: 1670, 1690 and 1750 µg/mL; mean AUC_t: 41800, 45400 and 43200 µg•h/mL; mean T_{max}: 0.083, 1 and 1 hour.

Potential additive effects of a combined treatment of subcutaneous administered marstacimab at 30 mg/kg once daily on day 1 and 8 and twice daily intravenous injections of FEIBA, a freeze-dried sterile human plasma fraction with Factor VIII inhibitor bypassing activity, at 10, 50, or 100 U/kg/day on day 8, 9 and 10 was investigated within the scope of the non-GLP compliant study 19GR258, which was conducted in male Wistar Han rats (5/group in main and 4/group in PK study). Vehicle groups for marstacimab and FEIBA were included and both test articles were also administered alone at the same doses as used in combination (marstacimab: 30mg/kg QD on D1 and D8; FEIBA: 10 (5 BID), 50 (25 BID), or 100 (50 BID) U/kg/day on Days 8-10). Subcutaneous administration of marstacimab at 30 mg/kg once daily on day 1 and 8 resulted in higher mean concentrations of thrombin-antithrombin complexes (TAT) (2.06x of vehicle control), but without any further test-article related findings (e.g. clinical, macroscopic and or microscopic observations).

Intravenous administration of FEIBA alone led to higher TAT concentrations, activated partial thromboplastin time and lower prothrombin time, correlating with clinical signs as well as macroscopic and microscopic observations (e.g. abnormal colour and increased incidence and/or severity of thrombi/emboli at the IV injection site, etc.) at the highest dose of 100 (50 BID) U/kg/day. Combined treatment of marstacimab and FEIBA showed similar results as reported for FEIBA alone, with the exception of higher TAT concentrations (2.30x-10.84x of vehicle control), slightly higher mean platelet volume values (1.05x-1.11x of control) and no increased incidence for test article-related thrombi/emboli in the lung, observed for concomitant treatment. Co-administration of marstacimab (30mg/kg QD) and FEIBA (5, 25 or 50 BID) did not alter systemic exposure of marstacimab, reflected by similar C_{max} , T_{max} and AUC_{48} values when dosed alone (marstacimab at 30mg/kg: day 1: 196 μ g/mL, 72hrs and 4100 μ g*hrs/mL, respectively; day 8: 219 μ g/mL, 48hrs and 7990 μ g*hrs/mL, respectively). Accumulation ratios of mean AUC_{48} values after marstacimab administration with and without combined treatment of FEIBA at various doses ranged from 1.8 to 2.1.

In the non-GLP compliant study 22GR075, potential additive effects of a combined treatment of subcutaneous administered marstacimab at 30 mg/kg once daily on day 1 and 8 and intravenously dosed Byclot, a freeze-dried activated human blood coagulation factor VII concentrate containing factor X, at 60 (30 BID), 120 (60 BID), or 180 (120/60 BID) μ g/kg/day on Day 8 and at 60, 120, or 120 μ g/kg/day QD on Day 10, were investigated in male Wistar Han rats (5/group in main and 4/group in PK study). Treatment with Byclot alone revealed shortened prothrombin times (0.45x-0.50x of respective control mean) and prolonged activated partial thromboplastin times (1.35x-1.51x of respective control mean) at all doses, whereas administration of marstacimab at 30 mg/kg alone did not result in any test-article related effects. Combined treatment of Byclot at all doses and marstacimab at 30mg/kg showed similar shortened prothrombin times and prolonged activated partial thromboplastin times (0.50x-0.52x and 1.45x-1.46x of respective control mean, respectively) as observed with Byclot alone, but led to an increase in thrombin:antithrombin-complex concentrations (1.41x-1.89x of respective control mean), which was not achieved by each individual treatment. Addition of various doses of Byclot did not alter mean systemic exposures (C_{max} and AUC) of marstacimab at 30mg/kg (marstacimab alone: day 1: C_{max} 156 μ g/mL, T_{max} 54hrs and AUC_{48} 4370 μ g*hrs/mL; day 8: C_{max} 140 μ g/mL, T_{max} 42hrs and AUC_{48} 4690 μ g*hrs/mL).

2.5.2.2. Secondary pharmacodynamic studies

No Secondary pharmacodynamic studies were performed with marstacimab.

2.5.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted, however safety pharmacology parameters were assessed within the scope of the GLP-compliant 13-week subcutaneous repeat-dose toxicity study in *Cynomolgus* monkeys (study 20062114), where no test article-related changes were observed in neurological parameters, respiration rate, ECG parameters and hemodynamic endpoints.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies, *in vitro* and *in vivo*, with available bypass agents as NovoSevenRT, FEIBA, or Byclot, were provided as part of the primary pharmacology section of this dossier.

2.5.3. Pharmacokinetics

Marstacimab PK/TK profile was characterised following intravenous (IV) and subcutaneous (SC) administration to rats (IV: 3-1000 mg/kg, SC: 3-180 mg/kg) and *Cynomolgus* monkeys (IV: 1-500 mg/kg, SC: 3-90 mg/kg).

Ligand-binding assays were used for quantification of marstacimab in rats and monkeys. Validated assays (in accordance to GLP) were used to support the bioanalysis of plasma samples from GLP toxicity studies. Validation reports were submitted and analytical methods used adequate for the measurement of marstacimab in plasma of rat and monkey, respectively.

For detection of anti-drug antibodies in plasma of rat and monkey, ligand-binding assays were validated based on the MSD assay platform. A rabbit anti-marstacimab anti-serum polyclonal antibody spiked into rat or *Cynomolgus* monkey plasma was used as positive control, while normal pooled rat or *Cynomolgus* monkey plasma, respectively, was used as negative control. Samples were tested using a tiered strategy (Screening, titre determination).

2.5.4. Toxicology

The Applicant filed a suite of toxicology studies. In total, five repeated dose toxicity studies, a male fertility and early embryonic development study, a weight of evidence carcinogenicity assessment, a local tolerance study, two immunotoxicity studies and two additional "other" toxicity studies were submitted. In general, this toxicology programme complies with recommendations in the current regulatory guidelines ICH M3(R2) and ICH S6(R1); justifications were provided for instances in which studies were waived.

2.5.4.1. Single dose toxicity

No single dose toxicity studies were submitted, as the toxicity profile of marstacimab was characterised in the repeated dose toxicity studies in rats and *Cynomolgus* monkeys in line with ICH M3(R2) and ICH S6(R1).

2.5.4.2. Repeat dose toxicity

In total, five repeated dose toxicity studies were submitted. At first, the toxicity profile and toxicokinetics of marstacimab were examined in a non-GLP compliant study in male Wistar Han (CRL:WI [HAN]) rats (n=5 per vehicle and dosing group, n=3 (vehicle) or 6 (test-article) in TK satellite groups) during and after two intravenous or subcutaneous administration (day 1 and 8 of the study) at 0, 3, 30 and 90 mg/kg/week and at 0 or 3 mg/kg/week, respectively (Study 13MA067). Similarly, in the non-GLP compliant Study 13MA070, the toxicity and toxicokinetics of marstacimab were evaluated in male and female *Cynomolgus* monkeys (n=1 per group and sex) that received 0, 3, 30 and 90 mg/kg/week marstacimab intravenously (bolus injection) and 0 and 3 mg/kg/week subcutaneously at day 1 and 8 of the study. Then, the toxicity and toxicokinetics of marstacimab were further examined in the GLP-compliant Study 20064198 in which male and female Crl:WI(Han) rats (n=10 per sex and vehicle/dosing group, and n= 3 (vehicle) or 6 (test-article) per sex and TK satellite group) received intravenous or subcutaneous marstacimab at 0, 60, 180 and 1000 mg/kg/week and 0 and 180 mg/kg/week, respectively. In this study, marstacimab was administered on a weekly basis for 3 months. Additionally, reversibility of potential test-article related effects was examined in the i.v. 0 and

1000 mg/kg/week groups after a 6-week recovery period. In the GLP-compliant Study 20089324, the toxicity and toxicokinetics of marstacimab were examined in male and female Crl:WI(Han) rats (n=15 per sex in vehicle and dosing groups, and n=3 (vehicle) and 4 (test-article) per sex in test-article TK satellite groups) via intravenous injections of 0, 60, 180, or 1000 mg/kg/week for 26 weeks. Also in this study, the toxicokinetics of the test-article was assessed in a follow-up test-article free 6-week recovery phase (only in the 60 mg/kg/week toxicokinetic cohort). Finally, in the GLP-compliant Study 20062114, marstacimab was administered to male and female *Cynomolgus* monkeys (n=3 per group and sex) at 0, 30, 90 or 500 mg/kg/week (i.v., slow bolus) and 0 or 90 mg/kg/week (s.c.) for 13 concomitant weeks. Reversibility of test-article related effects was examined in n=2 male and female 0 and 500 mg/kg/week animals after a 6-week period.

Marstacimab was very well tolerated in rats and *Cynomolgus* monkeys. Importantly, all test-article related effects identified in the repeated dose toxicity studies pertained to the pharmacologic mode of action of marstacimab (enhancement of the extrinsic clotting pathway) or the presence of marstacimab itself. In all studies, the highest applied doses (i.v. and s.c.) turned out to be the studies' NOAELs.

Specifically, decreases in fibrinogen, increases in D-dimer, prolonged activated partial thromboplastin time and increases in prothrombin time were generally observed in the animal toxicity studies, all of which were presumably related to the pharmacologic mode of action of marstacimab. Importantly, in the 6-month rat Study 20089324, marstacimab-related microscopic findings in the lung, specifically minimal acute and organizing thrombi/emboli, minimal infiltrates with refractile material, and minimal basophilic or non-basophilic foreign materials were observed. The occurrence of thrombi and emboli did not follow a dose-response relationship and did not lead to clinical and microscopic adversities in the affected animals.

Altogether, it therefore appears unlikely that these findings bear clinical relevance, especially considering the considerable supra-therapeutic exposures of marstacimab applied in this study. Additionally, similar microscopic findings were observed in vehicle control animals, potentially demonstrating that the rat model used in this study is susceptible to such micro-coagulation events, even in the absence of test-article. Apart from the lungs, also in the tail vein (the site of bolus injection) minimal acute and organising thrombi or emboli were identified and classified as test-article related. Again, these were characterised as non-adverse. Together with the considerable supra-therapeutic marstacimab doses used in this study, also no concern was raised on this finding.

Additionally, increases in globulin, total protein, and decreases in albumin:globulin ratios in both rats and *Cynomolgus* monkeys were correlated with the high amounts of administered marstacimab (being a IgG1 lambda antibody and a protein itself).

In terms of toxicokinetics, after intravenous administration, systemic marstacimab exposures increased with increasing dose, generally in a dose-proportional manner. No sex-specific differences in systemic exposure were observed, and maximally a small potential for accumulation was noted. After intravenous administration, marstacimab generally did not lead to the formation of ADAs. However, in Study 20064198, subcutaneous administration of marstacimab clearly led to an increased formation of ADAs. Finally, subcutaneous administration of marstacimab led to lower systemic exposures (in terms of Cmax and AUC₁₆₈) than intravenous administration of the same dose (e.g. rat Study 20064198).

Exposure margins were sufficiently large when compared to clinical exposures. Importantly, the subcutaneous clinical route of administration was only examined in some of the submitted non-clinical animal studies. However, also for this route of administration, sufficient exposure margins were realised, e.g. in the 3-month rat repeated dose toxicity Study 20064198 (5-fold exposure margin in the s.c. arm, and 212-fold exposure margin in the highest i.v. arm), and in the 3-month *Cynomolgus* monkey study (40-fold exposure

margin in the s.c. arm, and 219-fold exposure margin in the highest i.v. arm). The highest applied doses (i.v. and/or s.c.) translated to the NOAEs in all submitted studies, demonstrating a low toxicity potential of marstacimab in rats and *Cynomolgus* monkeys.

The absence of a 6-month repeated dose toxicity study in a non-rodent animal species (in the case of marstacimab a 6-month *Cynomolgus* monkey study) had prior to this MAA submission already been communicated with CHMP (in the scientific advice procedure EMA/H/SA/3363/1/2016/I, 21 July 2016). Even though ICH M3(S2) specifies that in the EU/EEA 6-months studies in rodents and non-rodents are required, ICH S6(R1) specifies that there might also be derivations from this principle when scientifically justified. Justification on this aspect was provided in the scientific advice procedure EMA/H/SA/3363/1/2016/I, 21 July 2016.

2.5.4.3. Genotoxicity

According to ICH S6(R1), genotoxicity studies were not performed.

2.5.4.4. Carcinogenicity

Standard carcinogenicity studies are not required for biotechnology-derived medicinal products as laid down in the Guideline ICH S6 (R1) EMA/CHMP/ICH/731268/1998. Instead, the decision for the need of carcinogenicity studies should be based on a case-to-case evaluation considering the biologic activity of the medicinal product.

Considering that Marstacimab is a monoclonal antibody, a direct pro-oncogenic effect is not anticipated. The Applicant states that a definitive link between TFPI and mechanisms of carcinogenesis has not been established but suggests potential of some tumour suppressive properties from literature references. Based on these data, it cannot be fully excluded that inhibition of TFPI could hinder these tumour suppressive effects. However, a thorough weight of evidence evaluation, in combination with data from the repeat dose toxicity studies, which included exposure to marstacimab up to 26 weeks, does not suggest any carcinogenic potential. Furthermore, marstacimab is expected to be administered intermittently (once weekly) in humans.

2.5.4.5. Reproductive and developmental toxicity

A male rat fertility and early embryonic development study (Study 00655204) was submitted. Haemophilia A and B are X-chromosome linked disorders are with extremely low prevalence in women, this non-clinical submission strategy has been accepted by CHMP in the EMA scientific advice procedure EMA/H/SA/3363/1/2016/I.

In Study 00655204, the potential effects of marstacimab on male fertility in Crl:WI(Han) rats after intravenous injection of 0, 60, 180 and 1000 mg/kg/week were assessed. Specifically, marstacimab dosing was initiated 4 weeks prior to mating, throughout mating, and was subsequently continued until euthanasia. During this period, 11 injections were administered. Per dosing group, n=20 male rats were used. Also n=20 marstacimab-naïve female rats (Crl:WI(Han) were used for determining the effects of marstacimab on siring performance and subsequently early embryonic development. Additionally, the toxicokinetics of marstacimab were examined (at exclusively 5 minutes post-dose).

No test-article related changes in male reproductive performance, spermatogenesis, embryonic survival and organ weights or macroscopic findings were observed. Consequently, marstacimab did not impose effects on male reproduction in Study 00655204.

In terms of juvenile toxicity, marstacimab will be indicated in patients of 12 years of age and older. Therefore, in principle, a juvenile toxicity study could be needed for adequately covering the non-clinical safety of marstacimab. However, the Applicant argued that in the 3-month repeat-dose toxicity Study 20062114 in *Cynomolgus* monkeys, the age of some of the animals aligned with the age of adolescent patients (monkeys were 3.7 to 7.2 years at dosing initiation).

2.5.4.6. Toxicokinetic data

See section 2.5.4.2. Repeat dose toxicity.

2.5.4.7. Local Tolerance

In line with the ICH S6(R1) guideline, local tolerance was assessed in a dedicated single dose SC study in rats and as part of the 6-month tail vein IV RDT study in rats. Injection site reactions, typical for mAb therapeutics, were observed after s.c. administration of marstacimab and were characterised by histopathological observations. These predominantly included minimal to mild mixed cell infiltration associated with minimal oedema and/or haemorrhage at the injection site, which were reversible, and slightly reduced food consumption which was not accompanied by any additional clinical signs, thus regarded as non-adverse. In addition, non-adverse test article-related microscopic findings of minimal acute and organizing thrombi/emboli at the tail vein IV injection site was observed at all doses in the 6-month rat repeat-dose toxicity study. No adverse local tolerance findings were observed in the 3-month rat RDT or the 8-day or 3-month monkey RDT studies at the IV or SC injection sites, respectively.

2.5.4.8. Other toxicity studies

Assessment of ADAs was conducted as part of the repeat-dose toxicity studies in rats and *Cynomolgus* monkey. ADAs were only observed in the 3-month rat study and did not impact on PK. Please refer also to the discussion provided on repeat-dose toxicity studies.

No C1q or Fc γ R binding was observed with marstacimab, suggesting a low potential to elicit CDC or ADCC activity. Marstacimab did not induce TNF- α , IL-6, or IFN- γ *in vitro*.

Studies on marstacimab metabolites have not been conducted. Marstacimab is expected to be metabolised by proteolytic catabolism and cleared by receptor-mediated and target-mediated mechanisms.

Studies on marstacimab impurities have not been conducted because of this type of medicinal product.

Besides staining with marstacimab in anticipated tissues in rat, monkey and human, TFPI expression was also found in the mesothelium, epithelium, and islet cells. However, it is agreed that *in vitro* binding of monoclonal antibodies to cytoplasmic sites is generally considered to be of low toxicological concern due to lack of *in vivo* relevance.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP guideline for Environmental risk assessment of medicinal products for human use" [EMEA/CHMP/SWP/4447/00 corr 2], as the proposed product falls within the classification of a products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) is not required.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Overall, the ***in vitro* primary pharmacology** program conducted by the Applicant is adequate to elucidate marstacimab's mode of action, being a fully human IgG1 monoclonal antibody directed against an epitope in the K2 domain of human Tissue Factor Pathway Inhibitor (TFPI), which is itself a Kunitz-type protease inhibitor, binding to Factor Xa via Kunits domain 2 (K2), and further triggering binding of this complex to Tissue Factor bound Factor VIIa via Kunitz domain 1 (K1). Inhibition of TFPI by marstacimab therefore leads to further Thrombin generation via the extrinsic pathway of the coagulation cascade, which is known to be not affected in patients with Haemophilia A (deficiency of FVIII) and B (deficiency of FIX).

The *in vitro* studies were performed using purified TFPI protein, non-haemophilic whole blood or plasma and haemophilic plasma.

In study PF-06741086_28APR15_072904, binding affinity and kinetics of marstacimab to human, mouse, rat, rabbit and *Cynomolgus* monkey TFPI K1K2 were investigated by Surface Plasmon Resonance (SPR) and binding was confirmed for each species in this assay. As it was published by Hansen *et al* 2014, that the monoclonal KPI-2 binding antibody concizumab cross reacted with rabbit TFPI but not with rat TFPI, the Applicant was asked for discussion regarding binding of marstacimab to rat TFPI K1K2, since this species had been used in non-clinical *in vivo* studies with marstacimab. To support the assumption that marstacimab is binding to rat TFPI, the Applicant provided further data in Memo 1 and Memo 2, indicating that concizumab and marstacimab are binding to different TFPI epitopes, by crystallography of TFPI-23 (the precursor of marstacimab) bound to *Cynomolgus* monkey TFPI K2 (which differs to human TFPI K2 by only two amino acids far from the TFPI-23 epitope), to the one of humanised 4F36 (a humanised mouse antibody on a human IgG4 Fc containing a sequence matching that of concizumab) bound to human TFPI K2 obtained from a NCBI structure database entry (Hilden *et al.*, 2012) (Memo 1). An overlap in contact residues was found twice (D102 and R107) but allows the antibodies to bind simultaneously since TFPI-23 and 4F36 bind TFPI-K2 from opposite sides. Furthermore, simultaneous binding of TFPI-23 and 4F36 huIgG4m to human TFPI (K1 and K2) was observed by surface plasmon resonance using a sandwich assay (Memo 2). Further SPR investigations endorsed binding to human TFPI K2 and non-binding to human TFPI K1 (study PF-06741086_14Nov22_121926).

A dose-dependent response of marstacimab to restore Factor Xa activity by inhibition of TFPI was shown in study PF-06741086_06APR15_085202. In the TF-FVIIa-FX Inhibition Reversal Assay a minor increase in Factor Xa activity was even observed in IgG control samples at higher concentrations. TEG analysis (study PF-06741086_01Apr15_142056) revealed dose-dependent changes in some clot formation dynamic parameter, indicating improvement in clot formation speed and strength.

Study PF-06741086_07APR15_123404 confirmed marstacimab's inhibitory effect on TFPI in the extrinsic pathway, leading to dose-dependent shortening of dPT clotting times in non-haemophilic human, rabbit and

Cynomolgus monkey plasma, increasing thrombin generation with increasing doses in non-haemophilic human plasma and no effect on aPTT clotting time, which is focused on the intrinsic pathway of the coagulation cascade. Similar results were obtained in severe haemophilia A (with and without inhibitor) and haemophilia B plasma samples (study PF-06741086_07APR15_135025), with EC50 values akin to the ones seen in non-haemophilic plasma of study 123404. Combination of marstacimab with rFVIIa further increased thrombin generation compared to rFVIIa alone, reaching non-haemophilic plasma control levels or even above. In this study (135025), the thrombin generation assay was performed in haemophilia A plasma from four different donors with increasing concentrations of marstacimab. In a separate assay, thrombin generation was investigated after addition of increasing doses of rFVII to haemophilia A plasma from donor GK-897-3292, with and without addition of 16 μ g/ml marstacimab. Untreated haemophilia A and normal plasma were used as control. No haemophilia A plasma with marstacimab alone was added for direct comparison with rFVII alone or combined treatment with marstacimab and rFVII in this assay, which would have been of interest in this context. When the same plasma from the severe haemophilia A donor Lot GK-897-3292 was used to determine the dose-response relationship for marstacimab, rFVIIa, and the combination of rFVIIa with a fixed 16 ug/mL concentration of marstacimab, not only the measured absolute values of lag time and peak thrombin were significantly different for the controls (lag time 23.08 min and 5.68 min; peak thrombin 3.2 nM and 38.4 nM) during the two measurements but also the effect size of 16 μ g/mL marstacimab: the lag time decrease was approximately 75% vs. 20%, and the peak thrombin increase was ~12-fold vs. ~4-fold. Literature data provided showed substantial susceptibility of thrombin generation assay for preanalytical errors explaining the observed large interexperimental variability. Additionally, it was shown that the inherent limitations of the thrombin generation assay were reduced by the coherent results of multiple independent non-clinical studies.

Table 2: Thrombin generation parameters in severe Haemophilia A plasma (GK-897-3292). Data from appendix 12.1, 12.8 and 12.9 in study report PF-06741086_07APR15_135025.

Lot No	table No in report 135025	marstacimab concentration (μ g/mL)	lag time (min)	peak thrombin (nM)
Lot GK-897-3292	12.1	0	23.08	3.2
Lot GK-897-3292	12.1	16	5.85	39.81
Lot GK-897-3292	12.8	0	5.68	38.4
Lot GK-897-3292	12.9	16	4.51	152.1

However, further extensive *in vitro* assays were conducted investigating concomitant dosing of marstacimab and rFVII (see study 122443 below). As mentioned above, in study 123404, the dilute prothrombin time (dPT) assay was conducted in human non-haemophilic human, rabbit and *Cynomolgus* monkey plasma, but not in rat plasma. Thrombin generation was investigated in human haemophilic inhibitor plasmas in the combination study 045123 with aPCC. Within the scope of the scientific advice from 2019 (CHMP Protocol Assistance, EMEA H SA 3363 3 20 18 PA III, 31 January 2019), the conduct of an *in vitro* study with rat plasma similar to that performed in human haemophilia plasma with activated prothrombin (study 045123) was proposed, to further help with the translation of any or the lack of effects seen *in vivo* in rats. Therefore, the Applicant was asked why haemophilic assays as dPT and TGA were not conducted with rat plasma, since this animal species had been used in *in vivo* combination studies with Byclot, FEIBA and Novoseven. It was then asserted that pharmacological activity of marstacimab in rats was sufficiently demonstrated *in vitro*, by assessing marstacimab's binding affinity to recombinant rat TFPI K1K2 (by SPR), as well as *in vivo*, since all test-article related effects observed in the repeated dose toxicity study in rats pertained to the pharmacologic mode of action of marstacimab.

Non-clinical evidence identifies marstacimab's mechanism of action in the well-defined extrinsic coagulation pathway: The two major coagulation pathways (intrinsic and extrinsic pathways) both ultimately lead to activation of Factor Z, which in turn leads to thrombin generation. FVIII and FIX form a single enzymatic complex and thus deficiency of either component, in patients with haemophilia A and B, respectively, manifests in similar coagulation deficits. In *in vitro* spike-in assays, marstacimab similarly promoted haemostasis in haemophilic plasma from haemophilia A, B, and haemophilia inhibitor plasma in haemostatic assays, including TGA. Consistent with this, an increase in thrombin generation in haemophilia a (with and without inhibitor) and haemophilia b plasma with increasing doses of marstacimab with or without co-treatment of rfviiia was observed in study pf06741086_31mar16_122443 as well, overall, obtaining physiological peak thrombin values, similarly as measured in untreated non-haemophilic plasma, at 16?g/ml marstacimab. combined treatment of marstacimab with a plasma derived activated prothrombin complex concentrate (apcc), at systemic exposures expected to occur after clinical administration, was investigated in study pf06741086_26jul18_045123, showing an additive increase in thrombin generation, even exceeding nonhaemophilic plasma control levels, but no additive decrease in lag time. study pf-06741086_14oct22_103228 investigated the effect of a possible combined treatment of marstacimab and byclot (fviia/fx), which resulted in, including but not limited to, an additive increase in peak thrombin, whereas a decrease in lag time was observed as well, but without any additive effect. overall, the concentration of 16?g/ml marstacimab used in various non-clinical *in vitro* assays was chosen to mirror expected cmax steady state concentrations following subcutaneous dosing of marstacimab at 2mg/kg, based on modelling. a comparable cmax (18.5?g/ml) was observed in the cynomolgus monkey study (number 8299672) after sc administration of marstacimab at 3mg/kg. similar values were reported following single dose subcutaneous administ

12870ng/mL in study B7841001 and B7841009, respectively) and patients with haemophilia (17110ng/mL and 15610ng/mL in study B7841002 and B7841010, respectively).

Overall, the performed *in vitro* studies provided evidence for selective and high affinity binding of marstacimab to the K2 domain of TFPI with broad species cross reactivity and for the increased activation of the extrinsic pathway in both non-haemophilic whole blood / plasma and haemophilia A and B plasmas without and with inhibitors. The combination of marstacimab and bypass agents in haemophilic plasmas (A and B) sometimes resulted in slight additivity in thrombin generation (peak thrombin level) but the concentration was within the range in studies reported for non-haemophilic normal plasmas. In this context it is worth to note that the intended clinical indication of marstacimab is prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors, or severe haemophilia without factor IX inhibitors.

Pharmacodynamic

Pharmacodynamic *in vivo* studies to assess non-clinical efficacy of marstacimab were conducted in *Cynomolgus* monkeys, Haemophilia A and B mice and Wistar Han rats.

Pharmacodynamics after repeated intravenous and/or subcutaneous dosing of marstacimab, observed as a decrease in dPT clotting time, and dose-dependent pharmacokinetics, correlating with target concentrations (total TFPI) in plasma, were investigated in male *Cynomolgus* monkeys in study 8299672. In group 1 animals, plasma concentrations of marstacimab after IV administrations of 1mg/kg marstacimab at day 1 were not quantifiable at 144 hours post-dose and therefore, animals receiving their second dose IV or SC of 3mg/kg on day 8 assumed to have no or negligible marstacimab concentrations prior to dosing. Animals of group 2, which received 10mg/kg IV marstacimab at day 1 still had high plasma concentrations of marstacimab at 168 hours post-dose and therefore prior to their second dose of 10mg/kg SC marstacimab on day 8. Recalculations of the PK parameters of the 10mg/kg SC marstacimab treatment group at day 8 using the pre-dose sample values taken from the prior time course (ie 168 hour) as C_0 instead of setting C_0 to 0.00 ng/ml as done before, showed to have no impact on evaluated PK parameters when compared to each other. Total TFPI concentrations in *Cynomolgus* monkey plasma increased with increasing concentrations of marstacimab and decreased with elimination of marstacimab. Because a strong correlation between free TFPI

and TFPI inhibitory mAb concentrations is expected in plasma, mirrored by a decrease of free TFPI with increasing concentrations of TFPI inhibitory mAbs (e.g.: Eichler H. et al, 2018; Chowdary P. et al, 2015) the Applicant was asked to provide data for free TFPI concentrations in *Cynomolgus* monkey plasma or discuss and justify the lack of those. A thorough explanation was provided by the Applicant that due to several reasons (observed issues due to e.g. sample dilution requirements, reagent competition leading to dissociation of TFPI from the drug-target complex and/or marstacimab's target affinity) efforts to develop an assay for the detection of free TFPI failed.

Haemophilia A and B mice were used as animal models of disease in study PF-06741086_07APR15_135244, where a dose-dependent reduction in blood loss after tail clip injury was observed, which was supported by the laser induced injury model in haemophilia A mice, where an increase in platelet accumulation and fibrin deposition was detected by intravital microscopy imaging. Results of study PF-06741086_31Mar16_121321, where further and similarly experiments in haemophilic mice were conducted, support the data from study 135244. The Applicant provided a rationale regarding the broad variation in sample sizes used in study 135244 and 121321, necessary to confirm marstacimab's mode of action and to support respective primary endpoints of each exploratory study. Haemophilia A and B mice were used as animal model of disease in study 135244 and 121321, which are generally considered an appropriate species for this purpose. Mice were dosed with intravenous marstacimab only, whereas the clinical route of administration, the subcutaneous route, was not investigated, neither in haemophilic mice, nor in other animal models of disease (e.g. haemophilic dogs or rabbits). (see also Clinical Efficacy discussion). However, the Applicant refers to the clinical study B7841001. In this trial pharmacodynamic effects and pharmacokinetics of marstacimab were investigated at different dose levels following subcutaneous (SC) or intravenous (IV) administration in healthy adults (first in-human study B7841001) and treatment related changes were observed for all PD endpoints (e.g. increases in total TFPI, peak thrombin, D-Dimer, and PF1+2 and shortening of TGA lag time and dilute prothrombin time) in both SC and IV treated subjects.

Study 16MA086 investigated the combined treatment of marstacimab with NovoSeven RT in rats. Concomitant administration of marstacimab and NovoSeven RT did not alter systemic exposures (C_{max} and AUC_t) 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. In study 19GR258, combined treatment of marstacimab and FEIBA was investigated and did not reveal any changes in systemic exposure (C_{max} and AUC_{48}) of marstacimab. Furthermore, combined treatment of marstacimab and FEIBA showed similar results as reported for FEIBA alone (e.g. increase in 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 in study 22GR075, 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, to summarise, treatment of rats with marstacimab alone led to no test-article related changes in Prothrombintime (PT), activated partial thromboplastin time (aPTT; as expected) and Thrombin-antithrombin complexes (TAT) 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. It is to note, that the use of marstacimab is indicated for the treatment of adult and adolescent patients with haemophilia A or B without inhibitors. 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. A concomitant study with FEIBA in rats was discussed within the scope of a scientific advice (CHMP Protocol Assistance, EMEA/H/SA/3363/3/20-18/PA- III, 31 January 2019), where the conduct of an *in vitro* study with rat plasma similar to that performed in human haemophilia plasma with activated prothrombin (study 045123) was proposed, to further help with the translation of any or the lack of effects seen *in vivo*. No such study was submitted with this MAA. Furthermore, scientific advice was provided in 2016 (CHMP Scientific Advice, EMEA H SA 3363 1 20161, 21 July 2016), where the use of marstacimab and eptacog alfa was discussed for the same purpose. It was pointed out by the CHMP, that any pivotal safety study should be conducted according to GLP, or thoroughly justified if not, that exposures should reflect clinical exposures and that the proposed number of animals (n=5/group) was thought to be minimal and could be adapted. In study 16MA086, group sizes remained 5 animals/group in the main study but were increased to at least 8 animals/group in the PK study arm. All combination studies with marstacimab were not conducted according to GLP.

Overall, the pharmacodynamic effect of iv or sc marstacimab in *Cynomolgus* monkeys was demonstrated by shortening of dPT with a stable decrease in dPT clotting time from 24 to 240 hours. Additionally, efficacy of intravenously administered marstacimab was shown in a model of disease, using acute tail clip injury and/or laser induced injury in haemophilia A and B mice. Combination studies in rats with marstacimab and bypassing agents (NovoSevenRT, FEIBA, or Byclot) were conducted to investigate the cumulative pharmacodynamics and potential additive effects of co-administration of these treatments. It is of note that these combination studies are relevant primarily in the context of patients with inhibitors but marstacimab's indication in this application is only for haemophilia A and B patients without inhibitors. In summary, the results of these *in vivo* combination studies did not raise major concerns regarding the combined effects of marstacimab and bypassing agents but with signs of enhanced efficacy for some combinations and doses.

Secondary pharmacodynamics

No dedicated secondary pharmacodynamic studies were conducted with marstacimab, since tissue cross-reactivity studies did not raise concern for any off-target effect, which is accepted.

Safety pharmacology

No dedicated safety pharmacology studies were conducted, whereat safety pharmacology parameters were assessed within the scope of the GLP-compliant 13-week subcutaneous repeat-dose toxicity study in *Cynomolgus* monkeys (study 20062114), where no test article-related changes were observed in neurological parameters, respiration rate, ECG parameters and hemodynamic endpoints.

Pharmacodynamic drug interaction studies

Pharmacodynamic drug interaction studies, *in vitro* and *in vivo*, with available bypass agents as NovoSevenRT, FEIBA, or Byclot, are covered in the primary pharmacology section.

Pharmacokinetics

Pharmacokinetics were determined after single and repeated dosing using SC and IV administration of marstacimab in rats and *Cynomolgus* monkey.

Several ligand binding assay methods were developed and validated for the determination of marstacimab concentration in rat and monkey plasma. A part of these validations was performed by the Applicant, and another part by CROs. The methods were validated according to the current requirements, including the quantification range, sensitivity, intra-batch and inter-batch precision and accuracy, dilutional linearity, selectivity, bench-top stability, long-term storage stability, freeze-thaw stability, and incurred sample

reanalysis (ISR). Out of the methods used for the determination of marstacimab in pivotal (GLP) toxicological studies, only the method 160918vlim-pgc was validated in accordance with GLP.

Ligand binding methods were also developed and validated for the detection of ADAs in rat and monkey plasma.

The methods used for the determination of PK/TK parameters were adequate for the assays (however, with further discussion of the non-GLP studies 13MA067 and 13MA070 studies - see below).

PK parameters were determined in a PK/PD study (Study number: 8299672) and in single and repeated dose toxicological studies (13MA067, 13MA070, 16MA86, 19GR258, 22GR075), following IV or SC administration.

The assays were performed at the same test site where the analytical methods were validated, thus no cross-validation was necessary.

Sufficient in-study validations were done, and the results were reported sufficiently, except in the 8299672 non-GLP PK/PD study, and in 13MA067 and 13MA070 non-GLP TK/PK studies. In the case of 8299672 PK/PD study the in-study validation data were not reported. The study reports of 13MA067 and 13MA070 PK/TK studies do not contain sufficient information about the methods used. However, the Applicant provided sufficient information on the methods in its answer to the questions.

The bioanalytical phases of the pivotal toxicological studies were carried out in accordance with GLP.

In 20089324 and 655204 studies the samples were analysed out of the long-term stability range determined within the method validation study (160918vlim-pgc), but sufficient stability of marstacimab during long-term freeze storage was determined in other method validation studies (e.g.: 15-1828 or 154029).

In *Cynomolgus* monkey the PK increased with dose and TMDD was observed at low doses. The mean t_{1/2} was between ~12 and 118 hours across doses in the nonclinical species.

Toxicokinetics were evaluated as part of the RDT GLP studies in rats and *Cynomolgus* monkeys.

Subcutaneous as well as intravenous administration of marstacimab was used. While accumulation was only observed in monkeys after repeated IV administration, systemic exposure after IV dosing increased dose-dependently in both species. No significant differences in PK parameters with regard to sex of the animals were observed in either species. Quantifiable levels of marstacimab were detected in rats through the recovery period in the 3- as well as the 6-month study, and in the 3-month RDT monkey study after 6 weeks of recovery.

ADAs were only observed in the 3-month rat study after SC dosing and at the lowest IV dose (60 mg/kg/week), but not at higher IV doses which may indicate that higher plasma levels of marstacimab may have interfered with ADA detection. However, ADAs did not appear to impact on marstacimab exposure in ADA-positive rats, as exposure was similar to ADA-negative animals. No ADAs were detected in monkeys.

PK was also evaluated in investigative pharmacodynamic studies in male rats to assess potential additive effects of combined, repeated dosing of marstacimab together with NovoSeven RT, FEIBA, or ByClot. The mean systemic exposure (AUC) was similar in all dose groups when marstacimab was administered alone or in combination with NovoSevenRT, FEIBA or ByClot. These data suggest there was no DDI effect on nonclinical PK after coadministration with these products.

Dedicated tissue distribution and protein binding studies were not conducted with marstacimab, which is agreed. Consistent with the known biodistribution of monoclonal antibodies, marstacimab showed low volume

of distribution, with V_{ss} of marstacimab in *Cynomolgus* monkeys ranging from ~34 to 65 mL/kg), suggesting a distribution to plasma and extravascular fluid commonly observed for IgGs.

No metabolism studies with marstacimab were conducted in animals. The absence of metabolism studies is in accordance with ICH S6(R1).

As marstacimab is a monoclonal antibody, it is expected to be proteolytically digested into peptides and amino acid. No specific studies to measure excretion of marstacimab were conducted. The absence of excretion studies in accordance with ICH S6(R1).

Dedicated drug-drug interaction studies were not conducted for marstacimab as DDI is not expected.

Pharmacodynamic studies in rats showed that the mean systemic exposure (AUC) after repeated dosing was similar in all dose groups when marstacimab was administered alone or in combination with NovoSeven RT, FEIBA or ByClot, respectively. These data further indicate no DDI effect on nonclinical PK after coadministration.

Toxicology

The toxicologic profile of marstacimab was adequately examined with the submitted studies and therefore generally supports marketing of marstacimab in the EU/EEA.

Importantly, no groups in which marstacimab was subcutaneously injected were included in the 6-month rat repeated dose toxicity Study 20089324 even though subcutaneous injection is the clinical route of administration. In general, repeated dose toxicity studies are expected to be carried out in the clinically intended route of administration. The lacking investigation of the repeated dose toxicity of marstacimab after subcutaneous administration in Study 20089324 could therefore – in principle – be problematic. Apart from regulatory considerations, this is e.g. supported by the fact that in the 3-month rat repeated dose toxicity Study 20064198, marstacimab was considerably more immunogenic after subcutaneous administration than after intravenous administration. Consequently, Study 20089324 did not adequately address the immunogenic potential of marstacimab in the rat after long-term (6 month) subcutaneous administration. Nonetheless, as already sufficient experience with subcutaneously administered marstacimab has been gathered in the clinical trials, it is not considered that an additional repeated dose toxicity rat study in which marstacimab would be subcutaneously administered for 6-months would add additional relevant information to the overall hazard characterisation and risk mitigation of marstacimab. Therefore, no concern was raised on this aspect.

Genotoxicity

Genotoxicity studies for marstacimab were not conducted; this omission is justified according to the ICH S6(R1) guideline.

Carcinogenicity

It is accepted that complete product-specific assessment of the carcinogenic potential of marstacimab was submitted in accordance with the requirements of ICH S6(R1) guideline. During scientific advice the CHMP agreed that a 2-year rodent carcinogenicity study is not warranted.

Based on the carcinogenicity risk assessment there are data suggesting tumour suppressive properties of TFPI *in vitro* and *in vivo* tumour models, there are no non-clinical or clinical reports of TFPI inhibition and increased cancer risk. In addition, no evidence for effects of TFPI inhibition on hormonal or immune modulation has been identified. Therefore, a definitive link between TFPI inhibition with intermittent administration of marstacimab and risk of carcinogenesis has not been established.

In the repeat-dose toxicity studies in rats and monkeys, there were no marstacimab-related proliferative/hyperplastic lesions or tumours, and no evidence of immunosuppression or immunostimulation, hormonal modulation, or chronic tissue injury. Further, there was no evidence of infection and there were no effects on any organ weight or microscopic findings in tissues/organs of the immune or endocrine systems. Therefore, marstacimab-related findings in the toxicity studies do not present a specific carcinogenicity concern. In summary, the weight of evidence indicates the carcinogenic risk of marstacimab is low and additional studies are not warranted.

Reproductive and developmental toxicity

The absences of other than male FEED studies in this submission is acceptable, no concerns were identified on the scope of the submitted developmental and reproductive toxicity studies. As no unexpected test-article related effects were observed in this study, marstacimab administration can be considered safe in adolescent patients. Additionally, the Applicant referred to literature and summarised that coagulation is already fully functioning 6 months post-partum. Therefore, adverse safety effects of marstacimab that would be specific to the adolescent patient population are not expected. These aspects are considered sufficient for waiving a juvenile animal toxicity study; it is not expected that such a study would contribute to a risk assessment in the adolescent patient population. The same conclusion had already been confirmed in prior consultations with EMA, specifically in the CHMP protocol assistance procedure EMA/H/SA/3363/3/2018/PA/III and the EMA PIP decision EMEA-002285- PIP02-19.

No test-article related changes in male reproductive performance, spermatogenesis, embryonic survival and organ weights or macroscopic findings were observed. Consequently, marstacimab did not impose effects on male reproduction in Study 00655204.

Local tolerance

No adverse local tolerance findings were observed in the 3-month rat RDT or the 8-day or 3-month monkey RDT studies at the IV or SC injection sites, respectively.

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.

Assessment of paediatric data on non-clinical aspects

This product is intended to be used in patients 12 years of age and older. Considering non-clinical aspects, a sufficient justification was provided why no juvenile toxicity studies were conducted.

2.5.7. Conclusion on the non-clinical aspects

Overall, marstacimab's mode of action, being a human monoclonal antibody directed against human Tissue Factor Pathway Inhibitor (TFPI), was demonstrated by *in vitro* and *in vivo* pharmacodynamic studies, with no concerns raised regarding safety pharmacology.

The PK/TK profile of marstacimab was adequately examined using validated ligand-binding assays. Potential induction of ADAs was investigated using the same assay system. The toxicologic profile of marstacimab was adequately studied. All relevant information has been reflected in sections 4.6 and 5.3 of the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant 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 3: Marstacimab Studies contributing Clinical Data

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen
B7841001	Phase 1 first-in-human, single ascending dose, randomised, double-blind, sponsor open, placebo-controlled study investigating the safety, tolerability, PK, and PD of SC and IV administration of marstacimab.	7 cohorts of healthy male adults and an additional cohort of healthy Japanese male participants. Randomised/Treated ^a /Completed: 41/41/40 Treatment by Cohort ^b (marstacimab/placebo): Cohort 1: 4/1 Cohort 2: 6/2 Cohort 3: 6/2 Cohort 4: 6/2 Cohort 5: 6/2 Cohort 8 (Japanese): 4/0	Presentation: Marstacimab solution for injection, 100 mg/mL vial Marstacimab or placebo <u>Marstacimab dose SC:</u> Cohort 1: 30 mg Cohort 2: 100 mg Cohort 3: 300 mg Cohort 8: 300 mg <u>Marstacimab dose IV^b:</u> Cohort 4: 150 mg Cohort 5: 440 mg
B7841002	Phase 1b/2 open-label study investigating the safety, tolerability, PK, PD, and efficacy of multiple SC doses of marstacimab.	Male adult participants (18 to <65 years) with severe haemophilia A or B with and without inhibitors to FVIII or FIX. Enrolled/Treated/Completed: 27/26/24 Treatment by Cohort: Cohort 1: 7 Cohort 2: 6 Cohort 3: 6 Cohort 4: 7	Presentation: Marstacimab solution for injection, 100 mg/mL vial Cohort 1 (non-inhibitor): 300 mg SC QW Cohort 2 (non-inhibitor): 300 mg SC loading dose, 150 mg SC QW Cohort 3 (non-inhibitor): 450 mg SC QW Cohort 4 (inhibitor): 300 mg SC QW
B7841003	Phase 2 open-label extension study of B7841002 assessing the safety, tolerability, and efficacy of marstacimab as a prophylactic treatment regimen.	Male participants with haemophilia A or B, with or without inhibitors to FVIII or FIX. Enrolled/Treated/Completed: 20/20/18 (2 de novo participants, 18 from Study B7841002) Treatment by Cohort: 300 mg SC QW: 10 150 mg SC QW: 10	Presentation: Marstacimab solution for injection, 150 mg/mL vial Doses: 150 mg and 300 mg QW Route of administration: SC
B7841005	Phase 3 one-way, cross-over, open-label, multi-center study. Treatment on factor replacement or bypass therapy during the 6-month Observational Phase is compared with a 12-month Active Treatment Phase.	Adolescent and adult participants between ages 12 to <75 years 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. <u>Non-inhibitor Cohort:</u>	Presentation: Marstacimab solution for injection, 150 mg/ml, PFS Marstacimab 300 mg SC for initial loading dose followed by 150 mg SC QW. Dose escalation to 300 mg SC QW allowed for participants meeting protocol-defined criteria.

		<p>Enrolled/Treated/Completed: Observational phase: 128/na/118 Active treatment phase: 116/116/111 Haemophilia A: n = 101 Haemophilia B: n = 27</p>	
B7841007	Phase 3 open-label extension study of B7841005 to evaluate the long-term safety, tolerability, and efficacy of marstacimab prophylaxis	<p>Participants with severe haemophilia A and B with or without inhibitors who completed Studies B7841005 or B7841008.</p> <p>Non-inhibitor Cohort: Enrolled/Treated/Completed: 88/87/na Haemophilia A: n = 67 Haemophilia B: n = 20</p>	<p>Presentation: Marstacimab solution for injection, 150 mg/mL, PFS and PFP Marstacimab 150 mg SC QW. Dose escalation to 300 mg SC QW allowed for participants meeting protocol-defined criteria</p>
B7841009	Phase 1 open-label, randomised, 4-period, 2 sequence, crossover study to evaluate the bioequivalence of marstacimab prefilled syringe and prefilled pen following single-dose subcutaneous administration.	<p>Healthy adult male participants. Randomised/Treated/Completed: 22/22/10</p>	<p>Presentation: Marstacimab solution for injection, 150 mg/mL, PFS and PFP Dose: 300 mg single dose Route of administration: SC</p>
B7841010	Phase 1 single-arm, open-label, non-randomised, non-controlled multicentre study to evaluate the PK, PD, safety, and tolerability of a single subcutaneous dose of marstacimab.	<p>Chinese adult participants with severe haemophilia. Enrolled/Treated/Completed: 6/6/6</p>	<p>Presentation: Marstacimab solution for injection, 150 mg/mL, PFS Dose: 300 mg single dose Route of administration: SC</p>

- a. Treated with study intervention; marstacimab for all studies except Study B7841001 which included placebo.
 b. Planned Cohort 6 (1000 mg IV) and Cohort 7 (2000 mg IV) were not evaluated in Study B7841001 as dose escalation was terminated as safety, tolerability, PK, and PD data through Cohort 5 was determined to be sufficient for progression to the next study (B7841002).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

PK results of phase 1 first-in-human Study B7841001 (single SC/IV dose in healthy adults)

Figure 1: Median Marstacimab plasma concentration-time profiles (linear scale) following administration of single SC or IV doses to healthy participants (B7841001)

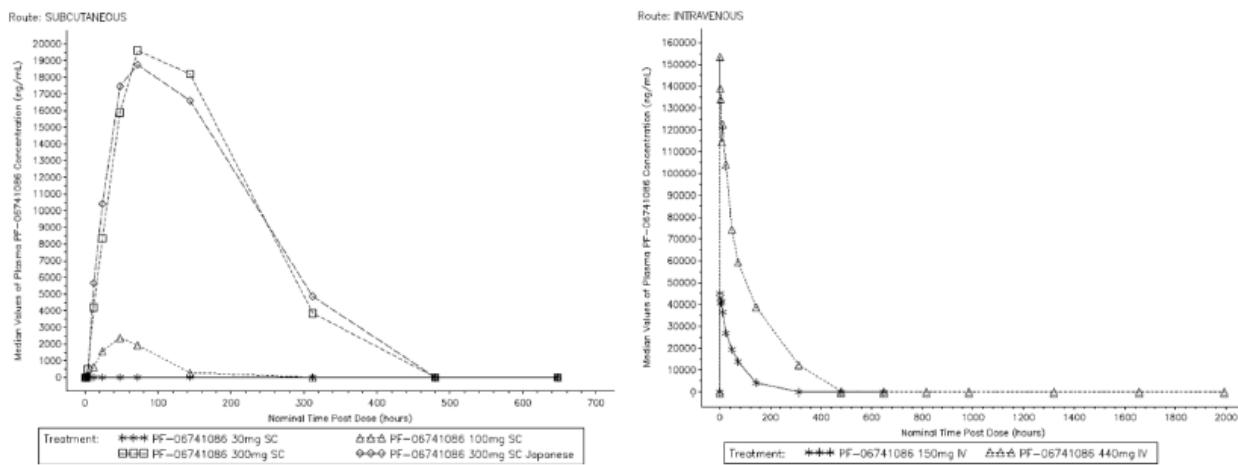


Table 4: Descriptive summary of plasma marstacimab pharmacokinetics parameters following single SC and IV doses (B7841001)

Parameter (units)	Parameter Summary Statistics ^a by Marstacimab Treatment Group					
	30 mg SC	100 mg SC	300 mg SC	300 mg SC Japanese	150 mg IV ^c	440 mg IV
N, n	4, 0	6, 4	6, 3	4, 2 ^b (4240000-5670000)	6, 6	6, 5
AUC _{inf} (ng*hr/mL)	NC	257700 (34)	2799000 (83)	4955000	2608000 (16)	14380000 (19)
AUC _{last} (ng*hr/mL)	0	81890 (391)	3120000 (68)	3551000 (28)	2346000 (14)	14290000 (21)
C _{max} (ng/mL)	0	1183 (287)	16490 (63)	18500 (25)	45640 (5)	152800 (12)
T _{max} (hr)	NC	48.0 (48.0-72.0)	72.0 (48.0-144)	108 (72.0-144)	1.07 (1.05-2.00)	1.54 (1.08-2.00)
t _{1/2} (hr)	NC	33.30 ± 5.39	65.77 ± 18.01	98.35 (74.7-122)	43.58 ± 4.95	79.46 ± 17.71
CL/F (L/hr)	NC	0.3878 (34)	0.1072 (83)	0.06185 (0.0530-0.0707)	NA	NA
CL (L/hr)	NA	NA	NA	NA	0.05750 (16)	0.03061 (19)
V _z /F (L)	NC	18.43 (31)	9.90 (107)	8.47 (7620-9310)	NA	NA
V _{ss} (L)	NA	NA	NA	NA	3.525 (8)	3.880 (17)

Source: Module 5.3.3.1 B7841001 – Table 14.4.4.1

N = number of participants contributing to the summary statistics, n = number of participants for t_{1/2}, AUC_{inf}, V_z/F (or V_{ss}) and CL/F (or CL), NA = not applicable, NC = not calculated

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± SD for t_{1/2}.

b. Median and range presented since N = 2.

c. The actual dose administered for Marstacimab 150 mg IV was 147 mg due to incorrect pump set and validation.

PK results of phase 1 Study B7841009 (single SC dose, 4-period, 2-sequence, bioequivalence comparing the PK of a pre-filled pen with a pre-filled syringe in healthy male adults)

Based on the statistical analysis performed using completer data ($N = 11$), PK of marstacimab administered via PFS versus PFP were demonstrated to be bioequivalent with test/reference ratios of adjusted geometric means of marstacimab AUClast and Cmax values of 107.5% (95.2%, 121.4%) and 104.1% (93.7%, 115.6%) respectively.

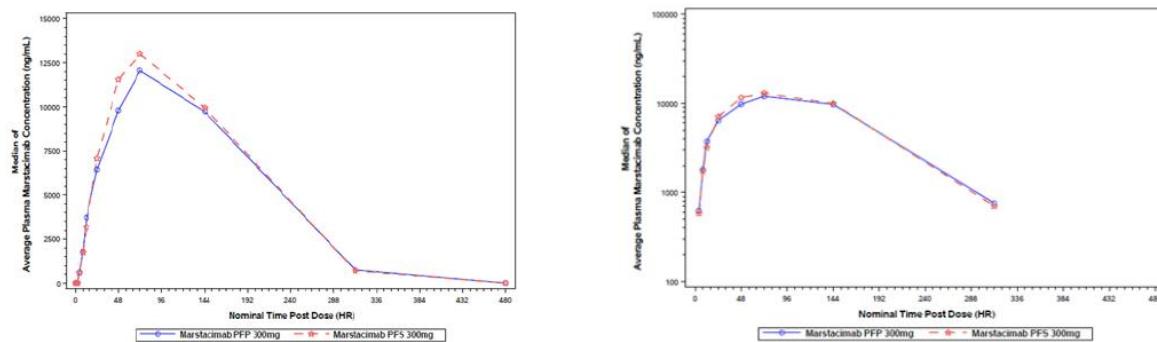
Table 5: Statistical summary of Log transformed plasma marstacimab PK parameters – PK parameter analysis set, participants who completed all 4 periods (completers), protocol B7841009

Parameter (Unit)	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Geometric Means ^a	90% CI (%) for Ratio ^a
	Marstacimab PFP 300mg (N=11) Test	Marstacimab PFS 300mg (N=11) Reference		
AUC _{last} (ng·hr/mL)	2275000	2116000	107.50	(95.20, 121.39)
C _{max} (ng/mL)	13480	12950	104.07	(93.70, 115.60)

Source: Table 14.4.5.3.
Natural log-transformed AUC_{last} and C_{max} were analyzed using a mixed effect model with sequence, period, treatment as fixed effects.
PK parameter analysis set was defined as all participants randomized and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period.
Values had been back-transformed from the log scale.
a. The ratios (and 90% CIs) were expressed as percentages.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2022 (05:06) Source Data: adpp Table Generation: 26JAN2022 (05:09)
Output File: ./nda1 cdisc/B7841009 PK2/adpp s201 im

Sensitivity analysis ($N = 15$) also showed the geometric mean ratios (test/reference) of AUClast and Cmax for $N = 15$ to be completely contained within the 80% - 125% acceptance criteria for BE (AUClast: 111.9% [101.1%, 123.9%] and Cmax: 107.7% [98.8%, 117.5%]).

Figure 2: Median marstacimab plasma concentration-time profiles (linear and semi-Log scales) by treatment group following single dose SC administration of 300 mg marstacimab to healthy participants using PFS and PFP (B7841009)



PK concentration analysis set was defined as all participants randomized and treated who had at least 1 concentration in at least 1 treatment period.
The lower limit of quantification was 100 ng/mL. Unplanned visits were not included in this presentation.
Averages of PK concentration values for replicate treatment have been used in this figure; averages are calculated by setting concentration values below the lower limit of quantification to zero.
Summary statistics have been calculated by setting averages of concentration values below the lower limit of quantification to zero.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2022 (05:06) Source Data: adpp Table Generation: 26JAN2022 (05:09)
Output File: ./nda1 cdisc/B7841009 PK2/adpp_s201_1

PK concentration analysis set was defined as all participants randomized and treated who had at least 1 concentration in at least 1 treatment period.
The lower limit of quantification was 100 ng/mL. Unplanned visits were not included in this presentation.
Averages of PK concentration values for replicate treatment have been used in this figure; averages are calculated by setting concentration values below the lower limit of quantification to zero.
Summary statistics have been calculated by setting averages of concentration values below the lower limit of quantification to zero.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2022 (05:06) Source Data: adpp Table Generation: 26JAN2022 (05:09)
Output File: ./nda1 cdisc/B7841009 PK2/adpp_s201_2

Table 6: Descriptive summary of average plasma marstacimab PK parameters – PK parameter analysis set, protocol B7841009

Parameter (Unit) ^a	Marstacimab PFP 300mg (N=18)	Marstacimab PFS 300mg (N=18)
N2, N3	18, 15	18, 13
AUC _{inf} (ng*hr/mL)	2523000 (56)	2482000 (49)
AUC _{last} (ng*hr/mL)	2018000 (69)	2015000 (50)
CL/F (L/hr)	0.1215 (57)	0.1218 (48)
C _{max} (ng/mL)	12550 (54)	12870 (43)
t _{1/2} (hr)	61.29 ± 20.073	60.24 ± 13.687
T _{max} (hr)	72.00 (60.0 - 146)	72.00 (60.0 - 146)
V _z /F (L)	10.19 (37)	10.21 (39)

Source: [Module 5.3.1.2 B7841009 – Table 14.4.5.1](#)
Averages of PK parameter values for replicate treatment had been used in this table.
N = total number of participants in the treatment group in the indicated population.
N2 = number of participants contributing to the summary statistics.
N3 = number of participants contributing to the summary statistics for t_{1/2}, AUC_{inf}, V_z/F and CL/F.
One participant was not included in this presentation.
PK parameter analysis set was defined as all participants randomised and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period.
a. Geometric mean (geometric CV (%)) for all except median (range) for T_{max} and arithmetic mean ± standard deviation for t_{1/2}.
PFIZER CONFIDENTIAL SDTM Creation: 26JAN2022 (05:06) Source Data: adpp Table Generation: 26JAN2022 (05:09)
Output File: ./nda1_cdisc/B7841009_PK2/adpp_s101_im

PK results of phase 1 Study B7841010 (single SC dose in adult Chinese haemophilia patients)

Table 7: Descriptive summary of plasma marstacimab PK parameters in Chinese Haemophilia participants following single dose SC administration of marstacimab 300 mg (B7841010)

Parameter (Unit) ^{a, b}	Marstacimab 300mg SC (N=6)
N2, N3	6, 4
AUC _{inf} (ng*hr/mL)	4549000 (7)
AUC _{last} (ng*hr/mL)	2917000 (60)
C _{max} (ng/mL)	15610 (35)
T _{max} (hr)	73.15 (71.9 - 167)
t _{1/2} (hr)	90.48 ± 26.025
CL/F (L/hr)	0.06595 (7)
V _z /F (L)	8.305 (29)

Source: [Module 5.3.3.2 B7841010 – Table 14.4.5.1](#)

PK parameter analysis set was defined as all participants treated who had at least 1 of the PK parameters.

N = Total number of participants in the actual treatment group in the indicated population.

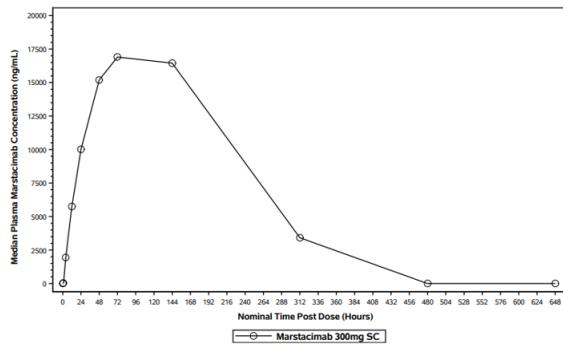
N2 = Number of participants contributing to the summary statistics.

N3 = Number of participants contributing to the summary statistics for AUC_{inf}, t_{1/2}, CL/F and V_z/F.

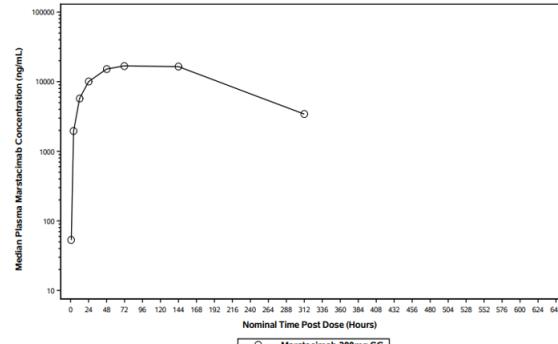
a. Geometric mean (geometric coefficient of variation (%)) for all except median (range) for T_{max} and arithmetic mean ± standard deviation for t_{1/2}.

b. C_{max} was included in the terminal phase to calculate k_{el} derived PK parameters AUC_{inf}, t_{1/2}, CL/F and V_z/F.

Figure 3: Median plasma marstacimab concentration-time profile (linear and semi-Log scales) in Chinese Haemophilia participants following single dose SC administration of marstacimab 300 mg (B7841010)



PK concentration analysis set was defined as all participants treated who had at least 1 concentration.
 Study planned visits DAY7, 14, 21, 28 located at ticks 144, 312, 480, 648.
 Summary statistics had been calculated by setting concentration values below the lower limit of quantification to zero.
 The lower limit of quantification was 100 ng/mL, setting concentration values below the lower limit of quantification to zero.
 PFIZER CONFIDENTIAL SDTM Creation: 11JAN2022 (2057) Source Data: adpc Table Generation: 12JAN2022 (22:29)
 (Database snapshot date : 02SEP2021) Output File: ./data1_cdisc/B7841010_PK/adpc_z01_im



PK concentration analysis set was defined as all participants treated who had at least 1 concentration.
 Study planned visits DAY7, 14, 21, 28 located at ticks 144, 312, 480, 648.
 Summary statistics had been calculated by setting concentration values below the lower limit of quantification to zero.
 The lower limit of quantification was 100 ng/mL, setting concentration values below the lower limit of quantification to zero.
 PFIZER CONFIDENTIAL SDTM Creation: 11JAN2022 (2057) Source Data: adpc Table Generation: 12JAN2022 (22:29)
 (Database snapshot date : 02SEP2021) Output File: ./data1_cdisc/B7841010_PK/adpc_z02_im

PK results of phase 1b/2 Study B7841002 (multiple SC doses in adult haemophilia patients)

Table 8: Descriptive summary of marstacimab plasma PH parameters (study B7841002)

Parameter (Unit) ^a	Marstacimab 300 mg SC Loading + 150 mg SC QW Non-Inhibitor ^c (N=6)	Marstacimab 300 mg SC QW Non-Inhibitor (N=7)	Marstacimab 450 mg SC QW Non-Inhibitor (N=6)	Marstacimab 300 mg SC QW Inhibitor (N=7)	Overall - Marstacimab 300 mg SC (N=14)
Day 1 (Week 1)					
n	6	7	6	7	14
AUC _{last} (ng*hr/mL)	2675000 (41)	1818000 (79)	2806000 (37)	2495000 (40)	2130000 (61)
C _{max} (ng/mL)	19480 (42)	14880 (70)	23070 (37)	19680 (51)	17110 (61)
C _{min} (ng/mL)	13040 (43)	7980 (112)	15660 (44)	11140 (41)	9429 (78)
T _{max} (hr)	69.7 (68.2, 71.1)	70.0 (69.1, 72.8)	71.6 (67.6, 72.3)	70.7 (22.8, 167)	70.1 (22.8, 167)
Day 29 (Week 5)					
n	6	5	4	5	10
AUC _{tau} (ng*hr/mL)	3309000 (50)	9045000 (49)	11090000 (43)	9248000 (38)	9146000 (41)
C _{max} (ng/mL)	24150 (44)	61850 (47)	73490 (38)	66070 (44)	63930 (43)
C _{min} (ng/mL)	15000 (59)	42120 (52)	53630 (61)	39490 (37)	40790 (42)
CL/F (mL/hr)	45.34 (50)	33.16 (49)	40.60 (43)	32.43 (38)	32.79 (41)
T _{max} (hr)	23.7 (22.0, 71.7)	23.7 (23.1, 94.2)	58.5 (23.3, 97.0)	22.8 (22.1, 94.7)	23.3 (22.1, 94.7)

	Marstacimab 300 mg SC Loading + 150 mg SC QW Non-Inhibitor^c (N=6)	Marstacimab 300 mg SC QW Non-Inhibitor (N=7)	Marstacimab 450 mg SC QW Non-Inhibitor (N=6)	Marstacimab 300 mg SC QW Inhibitor (N=7)	Overall - Marstacimab 300 mg SC (N=14)
Parameter (Unit)^a					
Day 85 (Week 13)^b					
n	5	6	6	5	11
C _{min} (ng/mL)	20630 (43)	57050 (58)	37310 (656)	61140 (51)	58880 (52)

Source: [Module 5.3.5.2 B7841002 - Table 14.4.5.2](#)

The dose of 1 participant was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the subject was analyzed in the Marstacimab 450 mg SC QW non-inhibitor dose cohort. The overall Marstacimab 300 mg SC group combined subjects from both the Marstacimab 300 mg SC QW non-inhibitor and inhibitor dose cohorts.

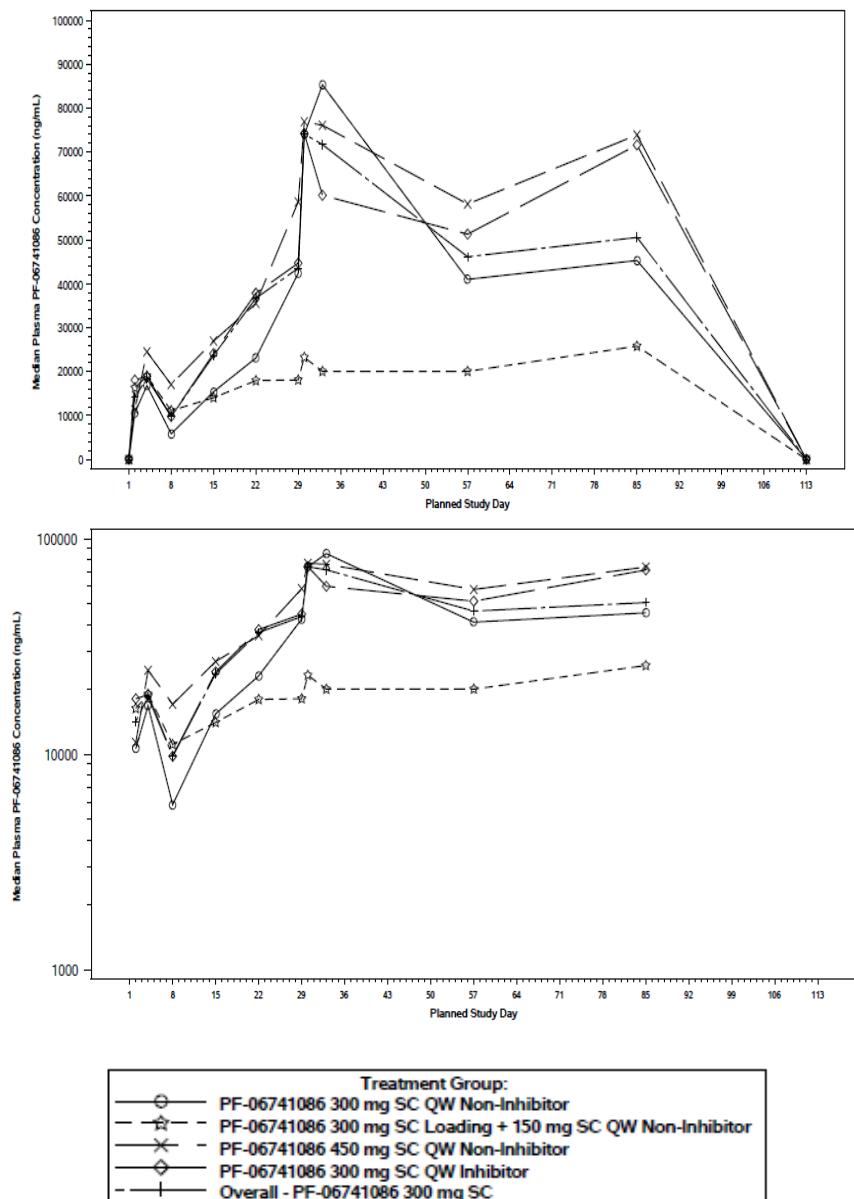
PK parameters for 4 subjects (1 subject from the Marstacimab 300 mg SC QW non-inhibitor dose cohort, 2 subjects from the Marstacimab 450 mg SC QW non-inhibitor dose cohort and 1 subject from the Marstacimab 300 mg SC QW inhibitor dose cohort) on Day 29 (Week 5) were excluded from the presentation.

a. Geometric mean (geometric %CV) for all except median (range) for T_{max}.

b. C_{min} of Day 85 (Week 13) represents plasma Marstacimab concentration of Day 85 (Week 13). Data points were excluded if there was a dose missed within 4 weeks prior to Day 85 (Week 13).

c. Day 1 (Week 1): 300 mg SC (loading dose); Day 29 (Week 5): 4th weekly dose of 150 mg SC following a loading dose of 300 mg SC.

Figure 4: Median Marstacimab Plasma Concentration-Time Profiles Following Single and Multiple Dose SC Administration of Marstacimab to Haemophilia A and B Participants With or Without Inhibitors (B7841002)



Upper and lower panels are linear and semi-logarithmic scales, respectively.

The lower limit of quantification was 100 ng/mL. Study Visit “Day 113/Follow-up” located at tick 113 on Xaxis.

The overall Marstacimab 300 mg SC group combined participants from both the marstacimab 300 mg SC QW noninhibitor and inhibitor dose cohorts.

Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0.

The dose of 1 participant was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the participant was analyzed in the marstacimab 450 mg SC QW non-inhibitor dose cohort.

PK concentrations for 4 participants (1 participant from the marstacimab 300 mg SC QW noninhibitor dose cohort, 2 participants from the marstacimab 450 mg SC QW non-inhibitor dose cohort and 1 participant from the marstacimab 300 mg SC QW inhibitor dose cohort) on Days 29, 30 and 33 were excluded from the presentation. Unplanned readings were excluded from this presentation.

PK results of phase 2 Study B7841003 (extension of Study B7841002)

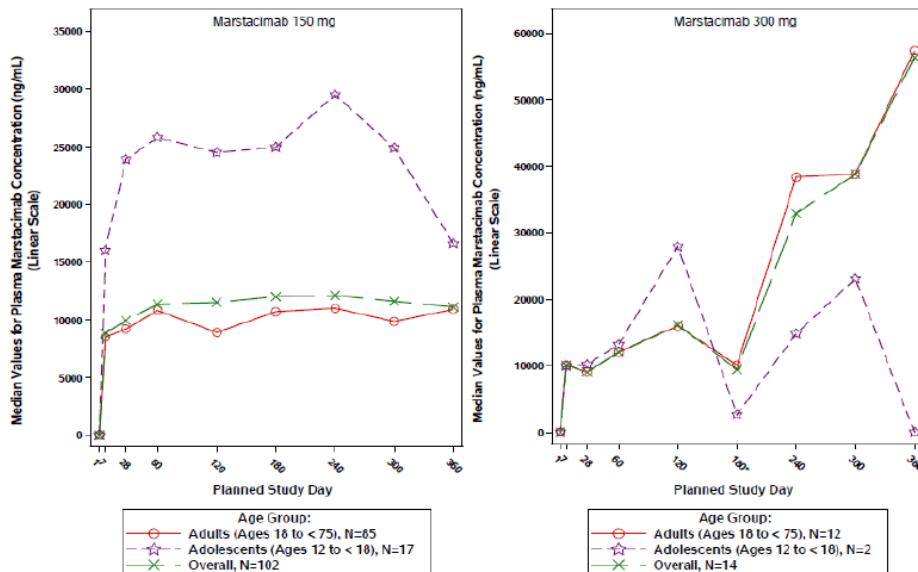
Marstacimab PK parameters for two newly enrolled participants were in agreement with those seen in Study B7841002.

PK results of phase 3 Study B7841005 (multiple SC doses in adult and adolescent haemophilia patients)

The 150 mg dose group consisted of participants who received 150 mg SC once weekly marstacimab throughout the entire study whereas the 300 mg dose group consisted of participants who were dose escalated to 300 mg SC once weekly marstacimab after Day 180 (Visit 14) following administration of 150 mg SC once weekly marstacimab up to that visit.

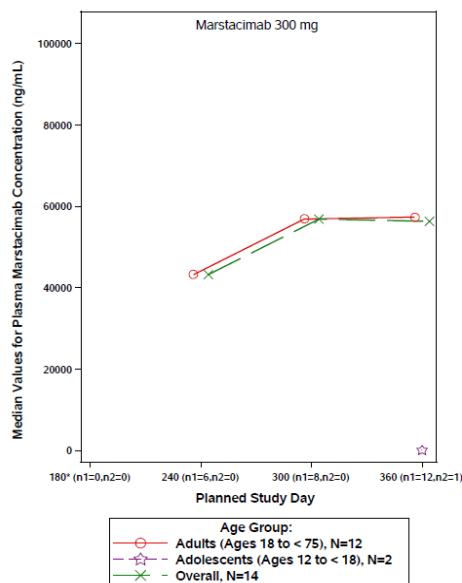
Following once-weekly subcutaneous administration of 150 mg, plasma concentrations of marstacimab appeared to have reached steady state by approximately 60 days (ie, by the 8th or 9th dose of weekly marstacimab dosing). Median steady-state marstacimab plasma concentrations in adults receiving 150 mg weekly were approximately 10,000 - 11,000 ng/mL whereas median steady-state marstacimab plasma concentrations in adolescents were approximately 25,000 – 30,000 ng/mL. For the most part, individual concentration-time profiles for adults and adolescents appeared to lie within a similar range of concentrations. In general, marstacimab concentrations are highly variable (% CV of approx. 62% - 92% in adults and 40% - 85% in adolescents for 150 mg SC QW).

Figure 5: Median marstacimab plasma concentration-time profiles (linear scale) following multiple dose SC administration of marstacimab to Haemophilia A and B participants without inhibitors (B7841005) by dose group and age group



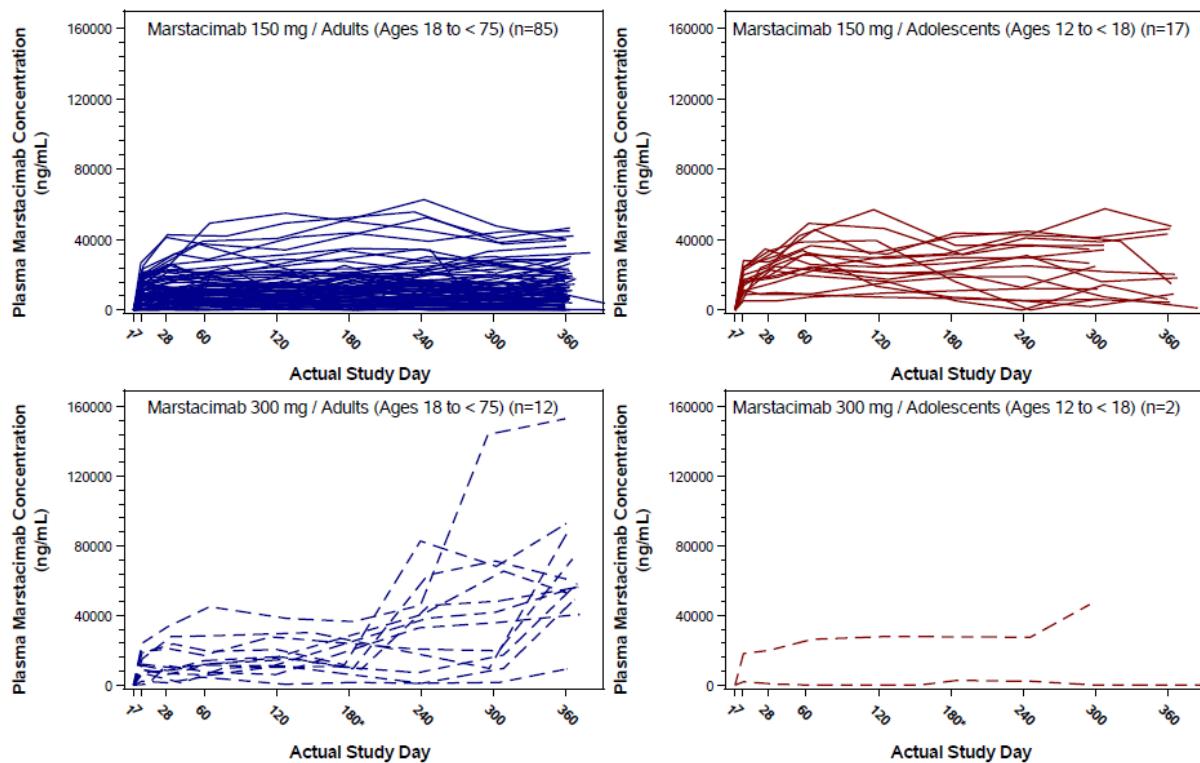
Marstacimab PK profiles in Figure 6 show summary data over the entire study duration based on categorization of participants by non-escalated (150 mg SC QW) and escalated (300 mg SC QW) dosegroups. To provide clarity for the 300 mg SC dose and take into account the different times at which dose escalation occurred, plasma concentration profiles starting from the time point of dose escalation only are shown in Figure 6A. Following escalation to 300 mg SC QW, in general, marstacimab concentrations are seen to be at or near steady-state.

Figure 6A. Median Marstacimab Plasma Marstacimab Concentration Versus Time Profiles by Age Group [Starting from the Time of Dose Escalation] for Dose-Escalated Participants Receiving Marstacimab 300 mg SC QW (B7841005)



N: Total number of participants in each age group.
 n1: Number of adult participants per analysis visit; n2: Number of adolescent participants per analysis visit.
 * Dose escalated to 300 mg on or after D180.
 Unplanned readings were excluded from this presentation.
 PFIZER CONFIDENTIAL SDTM Creation: 08JUN2023 (12:16) Source Data: adpc Table Generation: 19APR2024 (01:42) Output File: ./ndai_cdisc/B784_D80D120/adpc_f203_q65

Figure 7: Plot of individual plasma marstacimab concentration – time plot by dose group and age group (linear scale) – marstacimab safety set



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.

PFIZER CONFIDENTIAL SDTM Creation: 08JUN2023 (12:16) Source Data: adpc Table Generation: 15JUN2023 (01:26)
(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File: ./ndal_cdisc/B7841005_pkpd/adpc_f204

Bioavailability

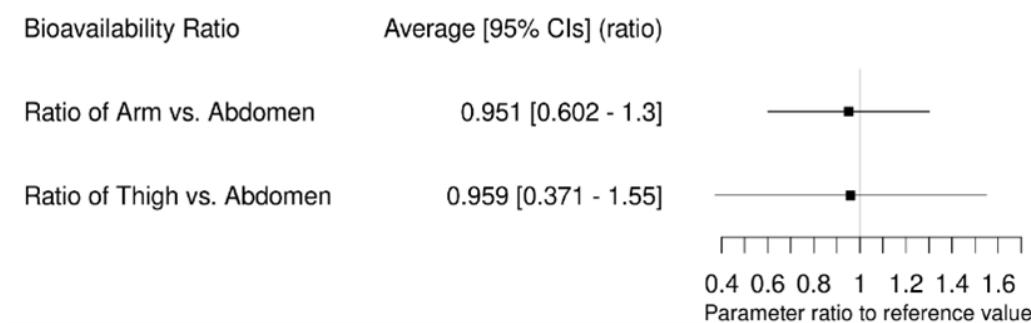
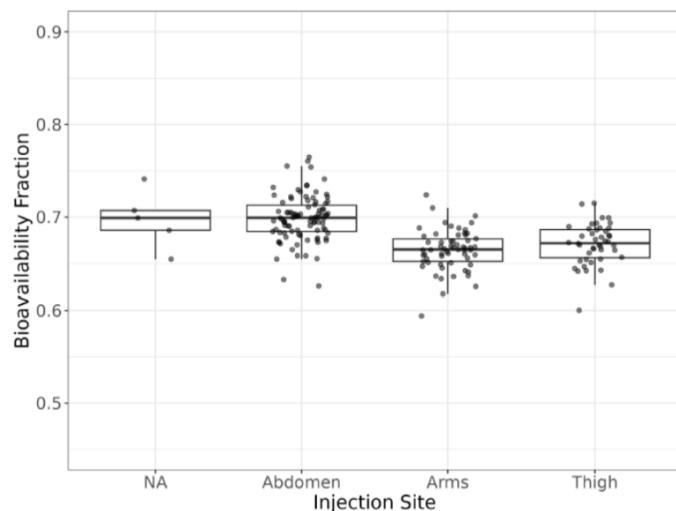
BA of SC dosing compared to the IV reference dose following single dose administration was 27%. Population PK analysis estimated marstacimab BA following SC administration to be approximately 71%. The multiplicative factor estimates for bioavailability for arm and thigh were both close to 1, ie 0.951 and 0.959 respectively, relative to the abdomen, resulting in bioavailability estimates of 67.0% and 67.6% for arm and thigh, respectively (based on $F_{abdomen}$ estimate of 70.5%) As such, no differences are seen in marstacimab bioavailability between arm and thigh. The difference in the BA estimate between single dose administration (NCA analysis) and multiple dose administration (pop 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-normalised AUCs following IV and SC may lead to significant under- or over-estimation of BA.

Table 9: Breakdown of injection sites for 150 mg dose group of B7841005

Injection Site	Percentage of Injections (%)
NA	0.2
Abdomen	67.6
Arm	20.7
Thigh	11.6

Repository artifact ID FI-44260141. Line 1 substituted.

NA represents the injections for which site of injection data was not available.

Figure 8: Forest plot of ratio of arm and thigh bioavailability as compared to abdomen**Figure 9: Empirical Bayesian estimates of bioavailability with site of injection**

N/A: Site of injection information not available

No statistically significant difference in bioavailability was detected, based on bioavailability ratios between abdomen vs. arms and abdomen vs. thigh.

Distribution

Following single dose IV administration in healthy participants marstacimab 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.

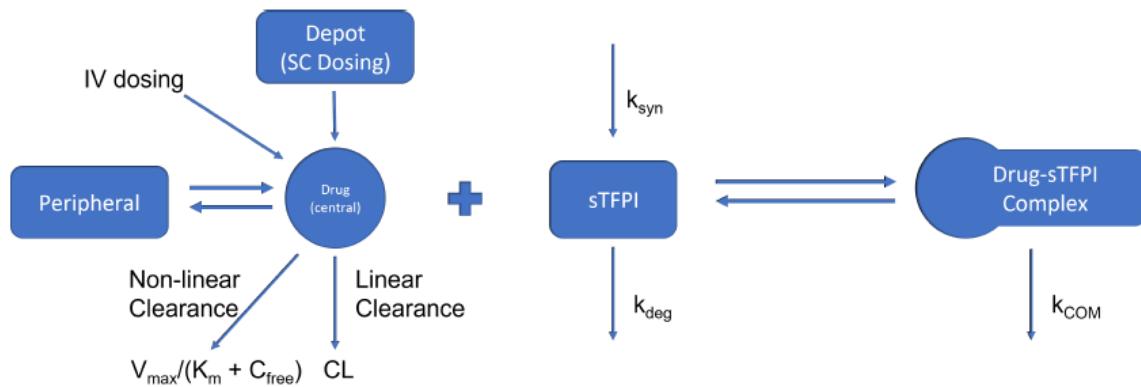
Population PK analysis estimates (%RSE) for central volume of distribution (V_c), peripheral volume of distribution (V_p) and volume of distribution at steady-state (V_{ss}) were 3.6 (9.2%) L, 5 (10.5%) L and 8.6 L, respectively. This limited extravascular distribution suggests that marstacimab is restricted to the intravascular space.

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 (Figure below).

Figure 10: Schematic of the final population PK model



The non-linear part was added to account for the drug binding to bound forms of TFPI. The estimated linear CL, Michaelis-Menten constant (K_m) for the drug's non-linear clearance and maximum saturable elimination rate (V_{max}) for the drug's nonlinear clearance (presented as population value (RSE%) in the final population PK analysis) were 0.019 (11.3%) L/hr, 4.31 (9.94%) nM and 0.53 (7.96%) nM/hr, respectively.

Marstacimab effective $t_{1/2}$ (geometric mean), calculated from the accumulation ratios, ranged from approximately 16 – 18 days across both adults and adolescents and across dose groups.

Dose proportionality and time dependencies

Following single dose administration to healthy participants in Study B7841001, under the same dosing route, exposures appeared to increase greater than proportionally with dose based on dose-normalized AUC_{inf} and C_{max} , which suggests that marstacimab may undergo target-mediated drug disposition.

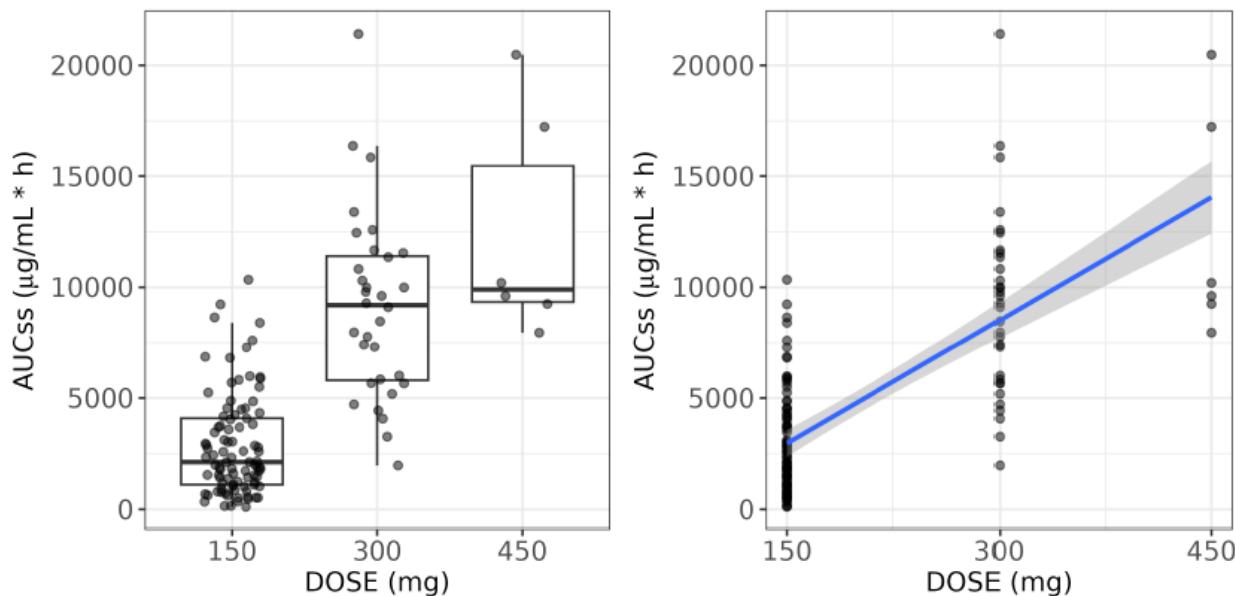
Population PK analysis using a power model [$AUC_{ss} = mDose^b$ or $\log AUC_{ss} = b * \log(Dose) + m$] as described by Wolfsegger et al was used to assess the dose proportionality of marstacimab in haemophilia patients over a range of 3 doses (150 mg, 300 mg and 450 mg). Results showed point estimate value of m (intercept) to be 5.47 (95% CI: 2.14 – 8.81) and point estimate value of b (the proportionality exponent or slope in the linearised equation) to be 1.81 (95% CI: -2.15 – 5.77). Based on the point estimate of 1.81 for slope (p -value = 0.1087), an approximately 3.5-fold increase in AUC_{ss} 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 AUC_{ss} in the 150 mg to 450 mg dose range.

Model-predicted estimates (median) for marstacimab AUC_{ss} in adults were 2110 µg*hr/mL (2.5 – 97.5 percentile: 214 – 8530 µg*hr/mL) and 9200 µg*hr/mL (2.5 – 97.5 percentile: 2970 – 17500 µg*hr/mL) for 150 mg SC QW and 300 mg SC QW respectively; approximately a 4.36-fold increase for a 2-fold increase in dose. Similar trends were also seen for model-predicted estimates of C_{max,ss}.

In general, marstacimab exposures (AUC_{ss} and C_{max,ss}) were seen to increase with slightly greater than proportional increases over the 150 mg to 450 mg SC dose range.

Figure 11: AUC_{ss} with Dosing Regimen for Dose Proportionality Analysis



AUC_{ss} is shown in mg/mL* hr units. Left panel shows AUC_{ss} as a box-plot with dosing regimens of 150 mg, 300 mg and 450 mg SC weekly dosing. Right panel shows the same as a line plot. The blue line represents the linear regression fit with standard error.

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

ADA and NAb were determined using validated bioanalytical methods.

Table 10: Overall incidence of anti-marstacimab antibody (ADA) and neutralising antibody (Nab) for phase 1b/2 studies B7841002/B7841003 and phase 3 studies B7841005/B7841007 – marstacimab dataset

Number (%) of Participants	Study B7841002/B7841003 (N=28)			Study B7841005/B7841007 (N=116)		
	ADA	NAb *	NAb #	ADA	NAb *	NAb #
ADA or NAb evaluable (N1)	28	3	28	116	23	116
Evaluable participants with pre-existing antibody, n/N1 (%)	0/ 28 (0.0)	0/ 3 (0.0)	0/ 28 (0.0)	2/116 (1.7)	0/ 23 (0.0)	0/116 (0.0)
Baseline-positive participants with nonboosted antibody response, n1/N1 (%)	0/ 28 (0.0)	0/ 3 (0.0)	0/ 28 (0.0)	2/116 (1.7)	0/ 23 (0.0)	0/116 (0.0)
Overall incidence, n2/N1 (%)	3/ 28 (10.7)	0/ 3 (0.0)	0/ 28 (0.0)	23/116 (19.8)	6/ 23 (26.1)	6/116 (5.2)
Treatment-induced	3/ 28 (10.7)	0/ 3 (0.0)	0/ 28 (0.0)	23/116 (19.8)	6/ 23 (26.1)	6/116 (5.2)
Treatment-boosted	0/ 28 (0.0)	0/ 3 (0.0)	0/ 28 (0.0)	0/116 (0.0)	0/ 23 (0.0)	0/116 (0.0)

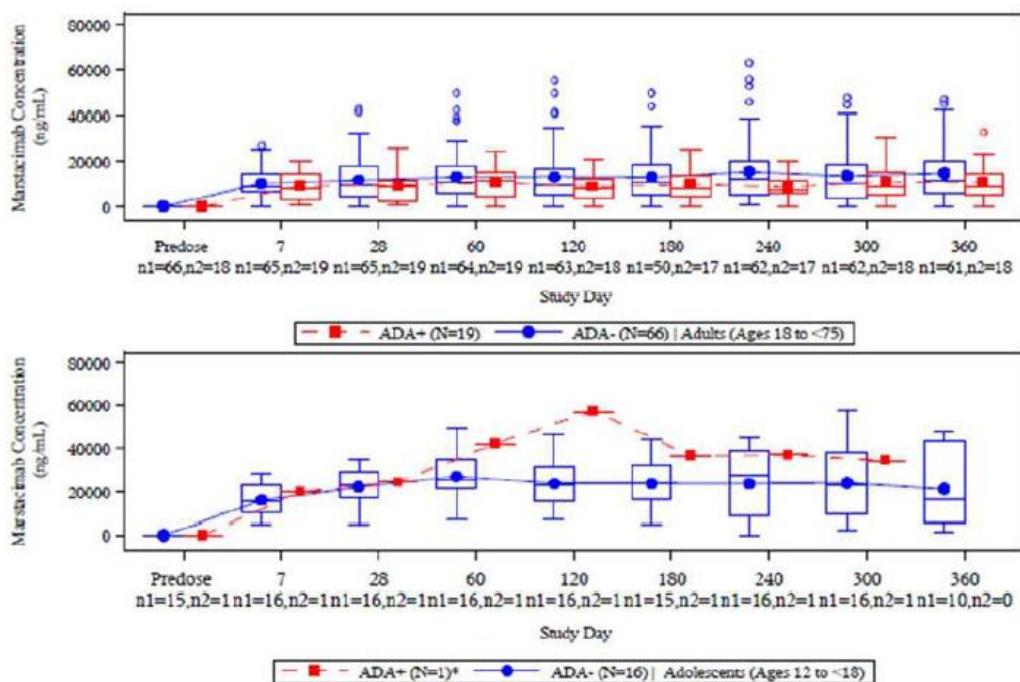
ADA+: ADA positive; ADA-: ADA negative; NAb+: Nab positive; NAb-: Nab negative.
Incidence is defined as the percent of ADA+ or NAb+ participants in a treatment group or trial.
ADA evaluable: All participants with ≥ 1 post-treatment ADA result.
NAb evaluable: ADA+ participants only with ≥ 1 post-treatment 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.
Baseline is defined as the last predose measurement.
N = Number of participants who received at least one dose of marstacimab; N1 = Number of ADA or NAb evaluable participants;
n = Number of ADA or NAb evaluable participants with positive ADA or NAb titer at baseline; n1 = Number of ADA or NAb evaluable participants with positive ADA or NAb titer at baseline but did not become boosted post-treatment; n2 = Number of ADA+ or NAb+ participants (treatment-induced or treatment-boosted).
*: NAb incidence relative to ADA+. #: NAb incidence relative to ADA evaluable.
PFIZER CONFIDENTIAL Source Data: adisda Table Generation: 11AUG2023 (06:15)
Output File: ./nda1_cdisc/B784_ISI_BLA/adisda_sp03

The data from the phase 1/2 trial do not allow any conclusions due to the small number of participants in relevant dose groups.

Marstacimab concentration time profiles (by age group) following weekly SC administration of 150 mg marstacimab to haemophilia participants from the Phase 3 study (B7841005) were compared between ADA positive and ADA-negative participants for assessment of differences in marstacimab PK between the 2 groups. Consistently lower mean/median marstacimab concentrations were reported in ADA-positive participants throughout all study visits.

Out of the 14 participants who dose escalated to 300 mg SC QW, only 3 were ADA positive (3 out of total 23 ADA positive; 2/21 adults and 1/2 adolescents). All 3 ADA-positive participants were ADA positive before dose escalation. None of the 14 dose escalated participants had new ADAs develop after dose escalation.

Figure 12: Boxplot of marstacimab plasma concentration vs time(150 mg) by ADA status by age for study B7841005 -marstacimab dataset



ADA+: ADA positive; ADA-: ADA negative. *Individual value only as N = 1.

The lower limit of quantification is 100 ng/mL.

N=Number of participants who had Marstacimab 150 mg dose and have respective ADA status.

n1=Number of ADA negative participants per analysis visit; n2=Number of ADA positive participants per analysis visit.

Filled squares: arithmetic mean for ADA positive; Filled circles: arithmetic mean for ADA negative.

Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range. Open circles represent individual values that were outliers (value outside of 1.5 times interquartile range).

PFIZER CONFIDENTIAL Source Data: adpc Date of Generation:21AUG2023(11:24)

Special populations

Population PK and PK/PD analyses were conducted using marstacimab PK (concentration) and PD (total TFPI and peak thrombin) data from all Phase 1 (B7841001, B7841009, B7841010), Phase 2 (B7841002, B7841003) and Phase 3 (B7841005) studies to evaluate the effect of relevant intrinsic and extrinsic factors ie, demographics, creatinine clearance, ADA status, on marstacimab PK and to support dosing regimens in various populations (eg, haemophilia type) 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 11: Parameter Estimates of the Final Population PK Model

Parameter	Population Estimate	SE	RSE/CV (%)	Bootstrap Estimate	Bootstrap 95% CI
Central Volume, V_c (L)	3.61	0.33	9.15	3.12	2.29-4.15
Linear Clearance, CL (L/hr)	0.0188	0.00212	11.3	0.0181	0.0118-0.0226
Inter-compartmental Flow, Q (L/hr)	0.00489	0.000501	10.2	0.00554	0.00389-0.0189
Peripheral Volume, V_p (L)	4.99	0.527	10.5	4.13	2.39-34.3
K_m for non-linear drug clearance, K_m , (nM)	4.31	0.429	9.94	3.56	1.78-4.6
V_{max} for non-linear drug clearance, V_{max} (nM/hr)	0.53	0.0422	7.96	0.605	0.377-0.81
Bioavailability Fraction, F	0.705	0.0314	4.44	0.69	0.554-0.744
Transfer rate from SC to Central compartment, K_a (1/hr)	0.00742	0.000541	7.29	0.00695	0.00583-0.00938
Baseline Total TFPI (nM)	3.75	0.0571	1.52	3.76	3.64-3.87
Degradation rate of free soluble TFPI, k_{deg} (1/hr)	0.0161	0.000921	5.72	0.0159	0.014-0.0186
Degradation rate of drug-TFPI complex, k_{com} (1/hr)	0.000754	9.31e-05	12.3	0.000694	0.000551-0.000928
Quasi-steady state constant, KSS	72.2	3.64	5.04	73.8	65.9-82.3
Lag-time (hr)	2	0.0449	2.25	1.98	1.23-2.59
Additive residual error on TFPI (log scale)	0.158	0.00154	0.971	0.157	0.143-0.174
Additive residual error on drug (log scale)	0.392	0.000991	0.252	0.391	0.341-0.444
Weight exponent on Central Volume	1.86	0.345	18.5	1.77	1.19-2.49
Weight exponent on Linear Clearance	1.14	0.365	32	1.15	0.568-1.71
Additional effect on CL for Healthy Population	0.199	0.211	106	0.163	-0.124-0.842
Additional effect on CL for Asian subjects	0.346	0.189	54.8	0.34	0.109-0.689
Additional effect on CL for ADA positive subjects	0.229	0.191	83.2	0.196	-0.0375-0.477
Additional effect on CL for Mild-renal impairment	-0.168	0.118	70.4	-0.152	-0.34-0.121
Additional effect on CL for Hemophilia B subjects	0.118	0.162	138	0.0881	-0.15-0.402
IIV on Central Volume, ($\omega_{V_c}^2$)	0.232	0.0819	48.1	0.162	0.0414-0.486
Correlation coefficient between IIVs for CL and V_c	-0.527	0.172	41.4	-0.113	-0.265-0.00799
IIV on Linear Clearance (ω_{CL}^2)	0.262	0.0592	51.2	0.246	0.126-0.407
IIV on Inter-compartmental Flow (ω_Q^2) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on Peripheral Volume ($\omega_{V_p}^2$) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on K_m ($\omega_{K_m}^2$) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on V_{max} ($\omega_{V_{max}}^2$)	0.101	0.043	31.8	0.105	0.02-0.29
IIV on Bioavailability fraction (ω_F^2)	0.0332	0.0585	18.2	0.0575	0.00106-0.208
IIV on K_a ($\omega_{K_a}^2$)	0.278	0.0504	52.7	0.201	0.116-0.405
IIV on Baseline TFPI (ω_{BTFPI}^2)	0.0249	0.00324	15.8	0.0249	0.0178-0.0325
IIV on K_{deg} ($\omega_{K_{deg}}^2$)	0.023	0.0183	15.2	0.0219	4.99e-05-0.215
IIV on K_{com} ($\omega_{K_{com}}^2$) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225
IIV on KSS constant (ω_{KSS}^2)	0.105	0.0301	32.3	0.105	0.0493-0.166
IIV on lag-time (ω_{LAG}^2) (fixed)	0.0225	0	15	0.0225	0.0225-0.0225

Bootstrap estimates were obtained from a bootstrap run with $N = 1000$ 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 thetaized (fixed) sigma parameter.

Table 12: Absolute and Weight-normalised Linear Clearance and Central Volume

Variable	Type 1	Type 2
Age Type	Adolescents	Adults
Subjects	19	131
Median CL (L/hr)	0.0143	0.0201
Difference in CL from Adults (%)	-28.8	.
Median Weight adjusted CL (CL/W) (L/hr/kg)	0.000279	0.000288
Difference in CL/W from Adults (%)	-3.13	.
Median Vc (L)	2.54	4.48
Difference in Vc from Adults (%)	-43.2	.
Median weight adjusted Vc (Vc/W) (L/kg)	0.0452	0.0609
Difference in Vc/W from Adults (%)	-25.857	.
Patient Type	Healthy	Hemophilia
Subjects	63	150
Median Weight adjusted CL (CL/W) (L/hr/kg)	0.000322	0.000287
Difference in CL/W from Hemophilia Subjects (%)	12.135	.
Race Type	Asian	Non-Asian
Subjects	64	86
Median Weight adjusted CL (CL/W) (L/hr/kg)	0.000326	0.000247
Difference in CL/W from Non-Asians (%)	31.934	.
Hepatic Impairment Type	Mild Impairment	None
Subjects	15	135
Median Weight adjusted CL (CL/W) (L/hr/kg)	0.000256	0.000288
Difference in CL/W from No Hepatic Impairment Subjects (%)	-11.1	.

CL - Linear Clearance (L/hr); Vc - Central Volume (L); CL/W - Weight adjusted Linear Clearance (L/hr/kg); Vc/W - Weight adjusted 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.

Table 13: Summary of Secondary PK Parameters by Dosing Regimen

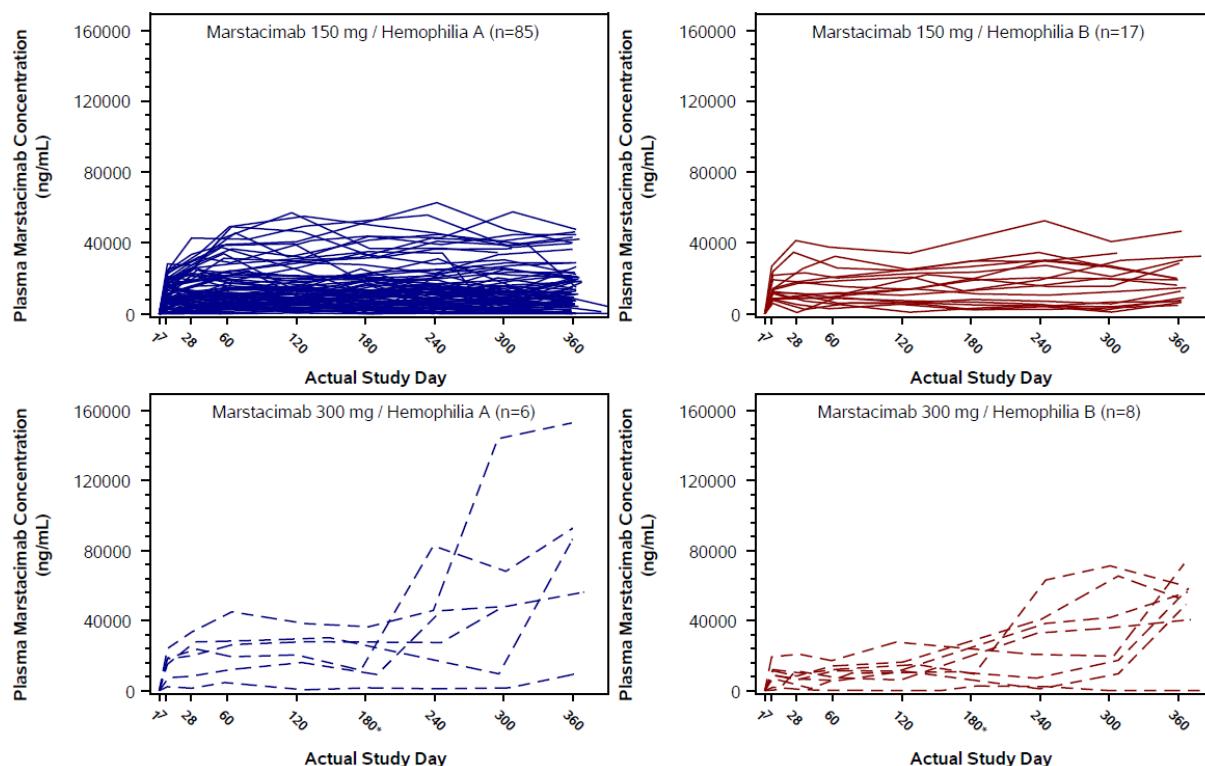
Parameter	150 mg (Adults)	300 mg (Adults)	150 mg (Adolescents)	300 mg (Adolescents)
Subjects (N)	99	32	17	2
Mean C _{min,ss} (ng/mL) (% CV)	13700 (90.4)	46500 (48.3)	27300 (53.2)	60700 (99.9)
Geometric Mean C _{min,ss} (ng/mL)	8320	41200	23400	42900
Median C _{min,ss} (ng/mL) (2.5 - 97.5%ile)	9400 (500 - 46000)	47300 (14000 - 94300)	28000 (8150 - 53000)	60700 (20000 - 101000)
Mean C _{max,ss} (ng/mL) (% CV)	17900 (77.5)	58200 (45.1)	34700 (48.5)	71700 (91.4)
Geometric Mean C _{max,ss} (ng/mL)	12800	52200	30500	54700
Median C _{max,ss} (ng/mL) (2.5 - 97.5%ile)	13600 (1710 - 53000)	57300 (19600 - 109000)	32400 (11400 - 62200)	71700 (27700 - 116000)
Mean C _{avg,ss} (ng/mL) (% CV)	16500 (81.2)	54200 (45.7)	32100 (49.5)	68100 (94.1)
Geometric Mean C _{avg,ss} (ng/mL)	11400	48500	28100	50900
Median C _{avg,ss} (ng/mL) (2.5 - 97.5%ile)	12600 (1280 - 50800)	54700 (17700 - 104000)	31300 (10300 - 59200)	68100 (25100 - 111000)
Mean AUC _{ss} (ng·h/mL) (% CV)	2770000 (81.2)	9100000 (45.7)	5390000 (49.5)	11400000 (94.1)
Geometric Mean AUC _{ss} (ng·h/mL)	1910000	8150000	4720000	8550000
Median AUC _{ss} (ng·h/mL) (2.5 - 97.5%ile)	2110000 (214000 - 8530000)	9200000 (2970000 - 17500000)	5260000 (1730000 - 9950000)	11400000 (4210000 - 18700000)
Mean ACCR (% CV)	4.86 (58.1)	4.72 (61.2)	4.88 (50.3)	3.94 (24.1)
Geometric Mean ACCR	4.19	4.14	4.32	3.89
Median ACCR (2.5 - 97.5%ile)	4.37 (1.42 - 12.5)	3.9 (1.8 - 11.3)	4.46 (1.7 - 10.1)	3.94 (3.31 - 4.58)
Mean effective t _{1/2} (days) (% CV)	21 (65.6)	20.3 (69.2)	21.1 (56.7)	16.6 (28)
Geometric Mean effective t _{1/2} (days)	17.1	17.1	17.9	16.3
Median effective t _{1/2} (days) (2.5 - 97.5%ile)	18.7 (3.95 - 58)	16.4 (5.98 - 52.6)	19.1 (5.48 - 46.4)	16.6 (13.5 - 19.7)

N- number of participants in the sub-group; SS - Steady State; ACCR - Accumulation Ratio Table 13 shows that the mean C_{min,ss}, C_{max,ss} and C_{avg,ss} were close to each other, indicating a low peak to trough ratio in drug concentrations at steady state for the 150 mg (Adults) and 300 mg (Adults) sub-groups.

Haemophilia Type

Population PK analysis did not show haemophilia type to be a clinically relevant covariate (11.8% higher CL in haemophilia B compared to haemophilia A; 95% CI: --15% to 40%); there were no relevant differences in marstacimab PK between haemophilia A and B patients.

Figure 13: Plot of individual plasma marstacimab concentration – time plot by dose group and haemophilia type (linear scale) – marstacimab safety set



Impaired renal function

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 = 128; eGFR \geq 90 mL/min/1.73 m²) or mild renal impairment (N = 22; eGFR of 60-89 mL/min/1.73 m²).

Population analysis of the effect of renal impairment on marstacimab CL showed a 16.8% lower CL with mild renal impairment (95% CI: -34% to 12.1%).

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

Impaired hepatic function

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 = 135, total bilirubin and AST \leq ULN) or mild hepatic impairment (N = 15, total bilirubin $>$ ULN, AST $>$ ULN). Mild hepatic impairment did not affect the pharmacokinetics of marstacimab. There are no data available on the use of marstacimab in patients with moderate or severe hepatic impairment.

Gender

Only male individuals were recruited for the trials. Considering that haemophilia is an X linked congenital bleeding disorder that affects almost exclusively males with very rare cases of female patients suffering from a severe form of the disease.

Ethnic factors

Effect of race on marstacimab PK was evaluated using population PK analysis with race as a covariate.

Population PK analysis showed that marstacimab CL (L/hr) was estimated to be approximately 35% (RSE of 54.8%) higher in Asian haemophilia participants. After adjusting for weight, marstacimab CL (L/hr/kg) was estimated to be approximately 31.9% higher in Asian participants.

Weight

Weight was an important covariate to describe the pharmacokinetics of marstacimab. Normalised 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 1.14 and 1.86 respectively.

Weight was able to account for most of the differences in PK between adults and adolescents, as described below. The studied weight range was 35 - 120 kg.

Paediatric population

Median steady-state marstacimab plasma concentrations in adults receiving 150 mg weekly were approximately 10,000 - 11,000 ng/mL whereas median steady-state marstacimab plasma concentrations in adolescents were approximately 25,000 – 30,000 ng/mL. For the most part, individual concentration-time profiles for adults and adolescents appeared to lie within a similar range of concentrations. In general, marstacimab concentrations are highly variable (% CV of approximately 62% - 92% in adults and 40% - 85% in adolescents for 150 mg SC QW).

The difference in marstacimab CL and Vc between adolescent and adult patient populations was approximately 29% and 43%, respectively, however, the weight-adjusted difference in CL and Vc between adolescents and adults was 3.1% and 25.9% respectively, indicating that weight explains most of the differences observed in CL between these two age groups.

Model estimated steady state Cmax,ss, Cmin,ss, Cavg,ss, AUCtau, accumulation ratio and effective t½ for marstacimab by age groups was presented. Accumulation ratio (geometric mean), calculated as ratio of AUC at steady state to the AUC for the first dose, was approximately 4 (across both dose groups and age groups).

Elderly

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 31 years (range: 13 – 66 years) and expected differences in marstacimab PK between adolescents and adults were mostly accounted by including weight as a covariate in the model.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	1	0	0

Pharmacokinetic interaction studies

Clinical PK DDI studies have not been conducted for marstacimab to date.

In vitro

In an *in vitro* human whole blood cytokine release assay, marstacimab did not elicit test article-related cytokine release of 3 human pro-inflammatory cytokines (TNF- alpha, IL-6, or IFN-gamma). Therefore, DDIs resulting from cytokine-mediated effects on CYP enzymes or transporters are not anticipated. Also, CYP enzymes are not anticipated to impact the clearance of marstacimab since the primary CL mechanisms of marstacimab are receptor-mediated endocytosis following binding to its target (TFPI) as well as regular IgG catabolism pathways. Thus, no risk of DDI is expected for marstacimab.

Many therapeutic proteins belonging to the cytokine class appear to differentially affect CYP activities.

Cytokine modulators may affect CYP enzyme activities by altering cytokine effects on CYP enzymes.

Marstacimab does not belong to the cytokine class. Marstacimab binds to the human TFPI K2 domain with low-nanomolar affinity, but it does not bind to the human TFPI K1 domain. It is therefore not expected to bind to cytokines and modulate their concentrations. Thus, changes in cytokine-dependent expression of CYP enzymes are not anticipated.

In vivo

In an investigative pharmacodynamic studies in rats, the mean systemic exposure (AUC) after repeat dosing was similar in all dose groups when marstacimab was administered alone or in combination with NovoSeven RT or FEIBA or ByClot. These data suggest there was no DDI effect on nonclinical PK after coadministration.

2.6.2.2. Pharmacodynamics

Mechanism of action

Marstacimab is a human monoclonal antibody directed against TFPI, the primary inhibitor of the extrinsic coagulation cascade. TFPI is a protease inhibitor which acts as an antagonist of the extrinsic coagulation pathway via inhibition of tissue FVIIa and FXa. Marstacimab inhibits TFPI and bypasses the need for replacement of FVIII or FIX. Marstacimab is capable of promoting haemostasis in human haemophilic plasma and in non-clinical models of haemophilia. The binding affinity (KD) of marstacimab for TFPI in human is 3.7 nM.

Non-clinical evidence identifies marstacimab's mechanism of action in the well-defined extrinsic coagulation pathway: The two major coagulation pathways (intrinsic and extrinsic pathways) both ultimately lead to activation of Factor X, which in turn leads to thrombin generation. FVIII and FIX form a single enzymatic complex and thus deficiency of either component, in patients with haemophilia A and B, respectively, manifests in similar coagulation deficits. In *in vitro* spike-in assays, marstacimab similarly promoted haemostasis in haemophilic plasma from haemophilia A, B, and haemophilia inhibitor plasma in haemostatic assays, including TGA.

Non-clinical efficacy demonstrates basis for effectiveness in bleeding control utilising the extrinsic coagulation pathway. The foundational nonclinical evidence is demonstrated in male haemophilia A (FVIII deficient) or haemophilia B (FIX deficient) mice in a severe tail clip injury model (a standard and validated [accepted] animal model in assessments of bleeding control). Marstacimab restored haemostasis in haemophilia mouse injury models when administered before and after the onset of a severe bleeding injury.

Based on the mechanism of action and pharmacology of marstacimab, the *in vivo* endpoints PF 1+2 and D-dimer, as well as the *ex-vivo* endpoints dPT and TGA (composed of thrombin generation lag time, endogenous thrombin potential (also referred to as endogenous thrombin generation potential) and peak thrombin [also referred to as TGA peak]) were monitored as pharmacologic effects reflective of coagulation pathway activation. Total plasma TFPI levels were measured to reflect target binding. Inhibition of TFPI is expected to be associated with an increase in PF 1+2, D-dimer, peak thrombin, and endogenous thrombin potential, as well as a shortening of dPT and thrombin generation lag time. An increase in total TFPI, due to binding of marstacimab with free TFPI thus resulting in delayed elimination of TFPI (bound to marstacimab), is also expected with the anti-TFPI pharmacology. The relationship between free TFPI and peak thrombin is inverse as free TFPI is highest at baseline (without any drug) and is expected to decrease as a result of marstacimab binding to TFPI.

Primary and Secondary pharmacology

PD in Phase 1 studies

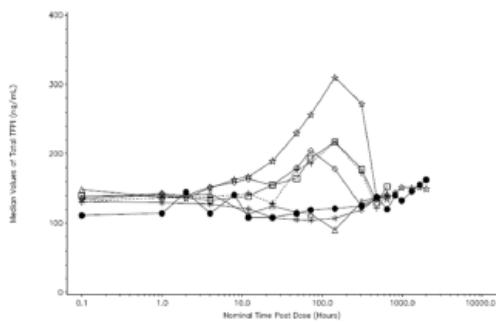
PD results of phase 1 first-in-human Study B7841001 (single SC/IV dose in healthy adults)

Following marstacimab SC and IV single dose administration, treatment related changes were observed for all PD endpoints and generally the response was exposure-dependent. These changes included increases in total TFPI consistent with binding of free TFPI with marstacimab, increases in PF 1+2, D-dimer, peak TGA, TGA endogenous thrombin generation potential, shortening of TGA lag time, and shortening of dPT.

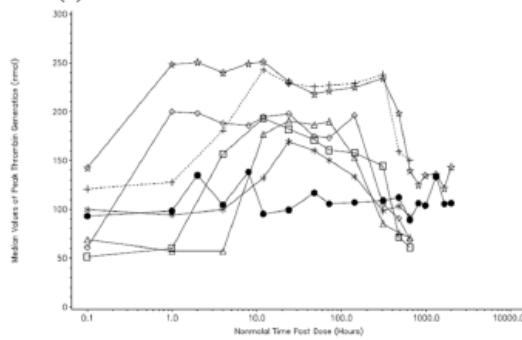
Pharmacologic effects on total TFPI as well as a number of PD biomarkers (eg, PF 1+2, TGA lag time and peak thrombin generation, and D-dimer) were seen to persist >7 days following administration of a single 300 mg SC dose. Weekly SC dosing was supported by effects seen on change from baseline calculated from Days 1-7. Effects were seen at all dose levels for some endpoints (eg, TGA lag time and TGA peak thrombin generation), and at a higher dose level for other endpoints (eg, D-dimer, PF 1+2 and dPT at 100 mg and above, and total TFPI at 150 mg and above). Maximum or near maximum effect occurred most frequently following a single dose of 300 mg SC based on values of maximum change from baseline as well as AUC.

Figure 14: Plot of median absolute values vs time for PF endpoints by cohort and dose following administration of single SC or IV doses of marstacimab to healthy participants (B7841001)

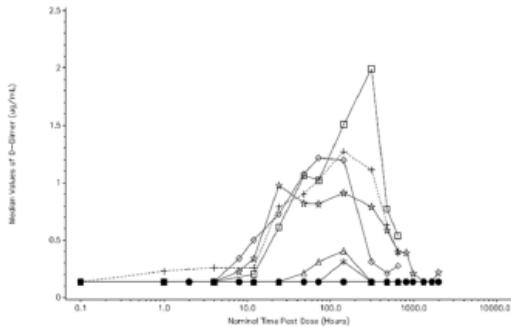
(a) Total TFPI



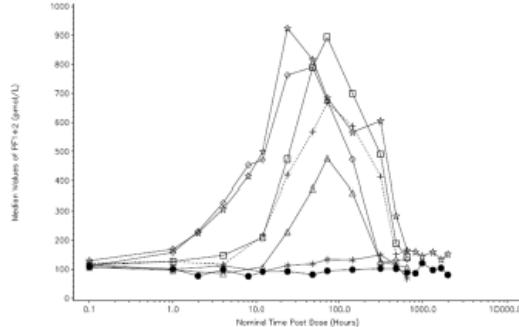
(b) Peak TGA



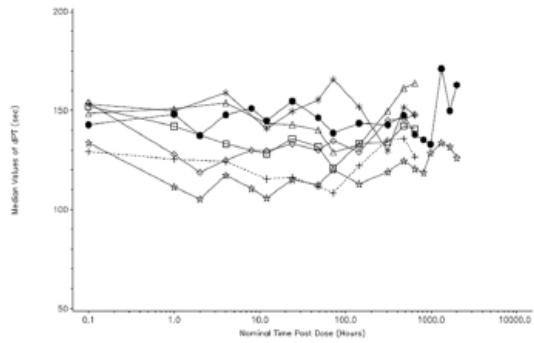
(c) D-dimer



(d) PF 1+2



(e) dPT



Treatment:	●●● Placebo	*** PF-06741086 30mg SC
	△△△ PF-06741086 100mg SC	□□□ PF-06741086 300mg SC
	◊◊◊ PF-06741086 150mg IV	★★★ PF-06741086 440mg IV
	++ PF-06741086 300mg SC Japanese	

PD results of phase 1 Study B7841010 (single SC dose in adult Chinese haemophilia patients)

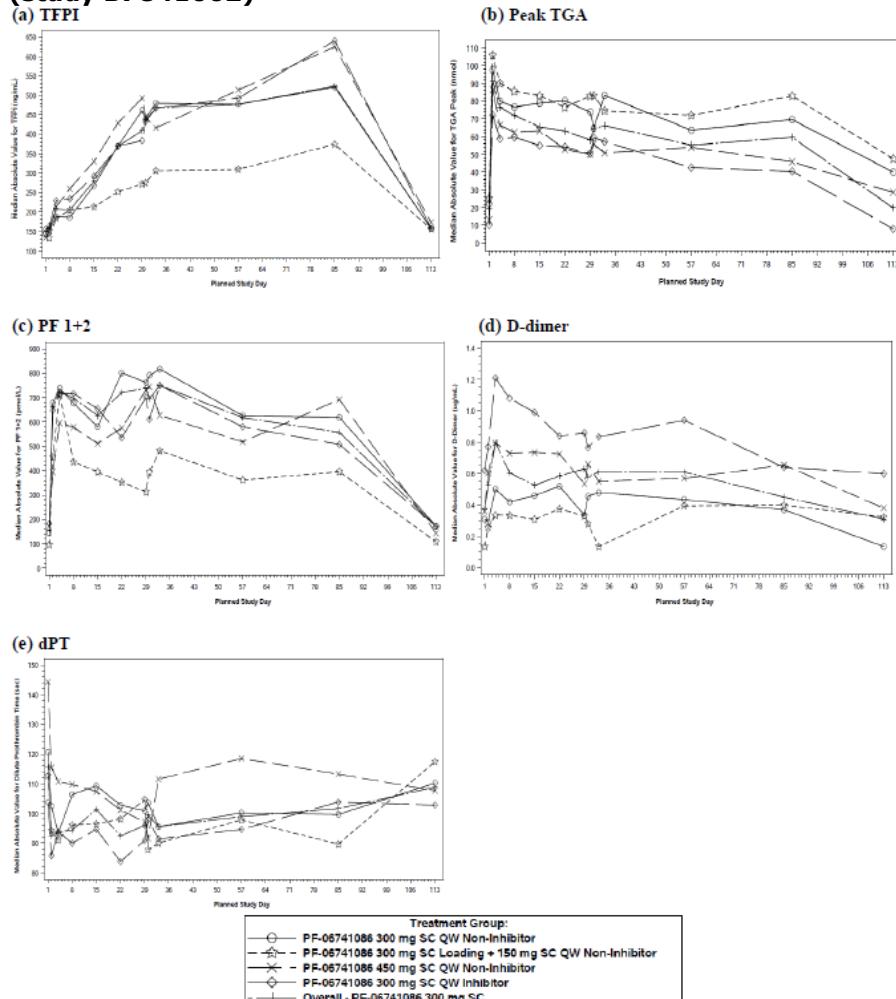
Following administration of a single SC dose of marstacimab 300 mg in Chinese participants with severe haemophilia A or B without inhibitors, treatment-related changes were observed for all PD endpoints. Increases were observed in plasma total TFPI, PF 1+2, D-dimer, peak thrombin, and TGA endogenous thrombin generation potential. A shortening of dPT and TGA lag time were also observed. Pharmacologic effects on total TFPI as well as all other PD biomarkers persisted >7 days following administration of a single

SC dose of marstacimab 300 mg. For all PD biomarkers, maximum or near maximum effect occurred most frequently within the first week based on maximum change from baseline.

PD in Phase 2 and 3 Studies

Treatment-related changes were observed for all PD endpoints in all dose cohorts as expected. These changes included increases in total TFPI consistent with binding of free TFPI with marstacimab resulting in delayed elimination of TFPI (bound to marstacimab) due to much longer half-life of marstacimab compared to the target TFPI, shortening of TGA lag time, increases in peak TGA, TGA endogenous thrombin potential, PF 1+2, and D-dimer, and shortening of dPT. There were no clinical findings suggesting that these PD changes were reflective of excessive pharmacology. PD responses were mostly consistent between participants with and without inhibitors and between participants with haemophilia A and B.

Figure 15: Plot of median absolute values vs time for PF endpoints following single and multiple dose administration of marstacimab to haemophilia A and B participants with or without inhibitors (study B7841002)



Source: Module 5.3.5.2 B7841002 - Figures 14.5.7.12, 14.5.2.12, 14.5.4.12, 14.5.5.12, and 14.5.6.12

Unplanned readings were excluded from this presentation. Follow-up samples were excluded if they were collected within 16 days after the last dose.

For D-dimer, the LLOQ was 0.27 µg/mL. All values below the LLOQ were imputed as $0.5 \times \text{LLOQ}$.

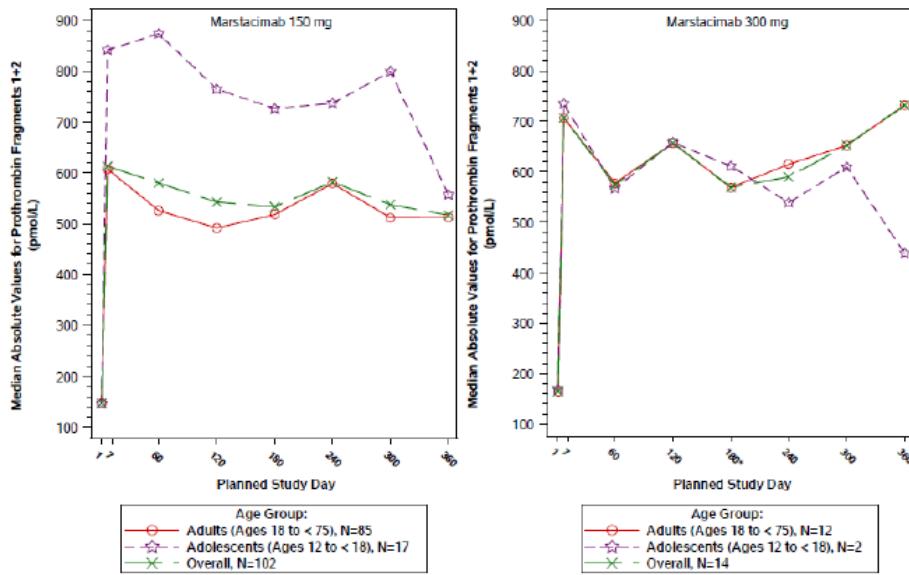
Study Visit "Day 113/Follow-up" located at tick 113 on X-axis.

The dose of 1 participant was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the participant was analyzed in the Marstacimab 450 mg SC QW non-inhibitor dose cohort.

Overall Marstacimab 300 mg SC group combined participants from both the Marstacimab 300 mg SC QW non-inhibitor and inhibitor dose cohorts.

b) PF 1+2:

Figure 17: Plot of median absolute values vs time for PF 1+2 (pmol/L) by dose group and age group (B7841005)



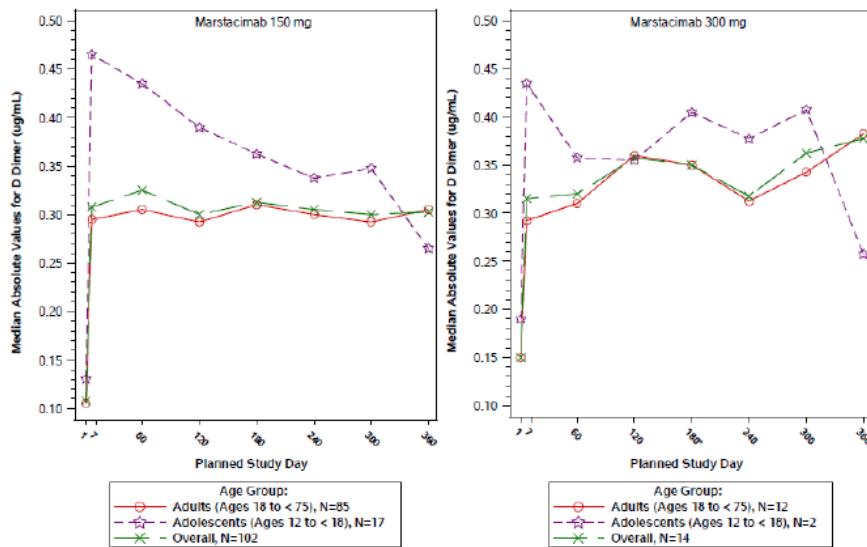
N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
* Dose escalated to 300 mg on or after D10.

PFIZER CONFIDENTIAL EDDM Creation: 23JUN2023 (16:41) SOURCE DATA: adpd Table generation: 26JUN2023 (23:33)
DATA CUTOFF DATE: 17APR2023 DATABASE SNAPSHOT DATE: 05MAY2023 OUTPUT FILE: ./nadal_cisec/B7841005_pkpd/adpd12.r001

Post-treatment variability (geometric %CV) in PF 1+2 data ranged from 25% - 99% across adults and adolescents (150 mg SC).

c) D-dimer:

Figure 18: Plot of median absolute values vs time for D-dimer (μ g/mL) by dose group and age group (B7841005)



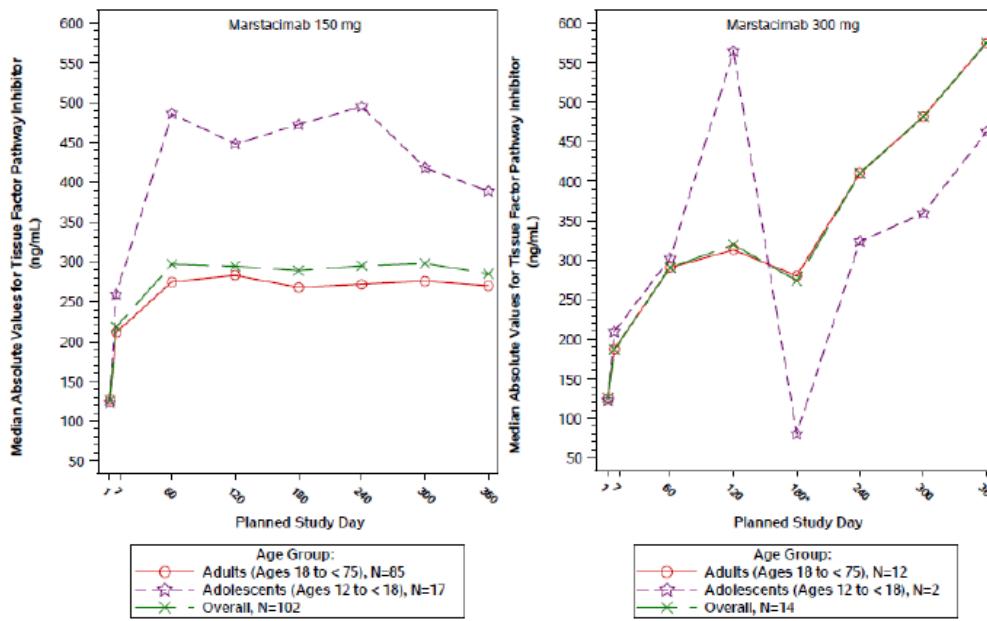
N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
* Dose escalated to 300 mg on or after D10.

PFIZER CONFIDENTIAL EDDM Creation: 23JUN2023 (16:41) SOURCE DATA: adpd Table generation: 26JUN2023 (23:44)
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Post-treatment variability (geometric %CV) in D-dimer data ranged from 40% - 76% across adults and adolescents (150 mg SC).

d) Total TFPI:

Figure 19: Plot of median absolute value vs time for Tissue Factor Pathway Inhibitor (ng/mL) by dose group and age group (b7841005)



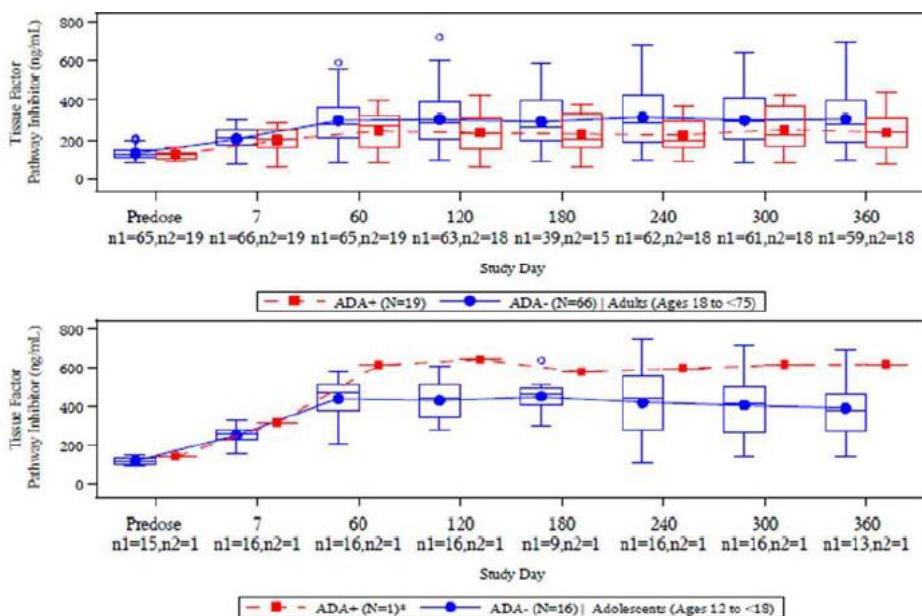
N: Total number of participants in each dose and age group.
Unplanned readings were excluded from this presentation.
Dose: Mean dose of 300 mg per day.
P: P-value of the primary comparison (SDIN2022 vs SDIN2023).
[Data cutoff date : 17ABR2023 database snapshot date : OEMAY2023] Output File : /nfs/citac/b7614105/prpd/adtrpt.f001

Post-treatment variability (geometric %CV) in TFPI ranged from 19% - 58% across adults and adolescents (150 mg SC).

Effect of ADA and NAb on PD Data

Profiles of key pharmacodynamic endpoints ie, TFPI (total), TGA peak, PF1+2, dPT and D-dimer following weekly SC administration of 150 mg of marstacimab to haemophilia participants from the Phase 3 study (B7841005) were compared between ADA positive and ADA-negative participants for assessment of differences in PD between the 2 groups (only TFPI data shown, Figure below). For adults, there were consistently lower mean and median values for TFPI concentrations in ADA positive subjects at nearly all study visits. The remaining PD parameters (peak thrombin, PF 1+2, D-Dimer) were more comparable between ADA positive and ADA negative participants.

Figure 20: Boxplot of Tissue Factor Pathway Inhibitor over Time (150 mg) by ADA status by age for study B7841005 – marstacimab dataset



ADA+: ADA positive; ADA-: ADA negative.

N=Number of participants who had Marstacimab 150 mg dose and have respective ADA status.

n1=Number of ADA+ participants per analysis visit. n2=Number of ADA- participants per analysis visit.

Filled squares: arithmetic mean for ADA+. Filled circles: arithmetic mean for ADA-.

Box plot provides median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range. Open circles represent individual values that were outliers (value outside of 1.5 times interquartile range).

*Individual value only as N = 1.

PFIZER CONFIDENTIAL Source Data: adpd Date of Generation:16AUG2023(08:05)

2.6.3. Discussion on clinical pharmacology

The submitted dossier includes PK/PD data from six clinical trials.

Healthy male adults were recruited for the phase 1 first-in-human single ascending dose Study B7841001 and for the phase 1 bioequivalence Study B7841009. **Study B7841001** investigated the PK/PD of Marstacimab at different dose levels (30 to 440 mg) in 6 cohorts with either SC or IV administration (cohort 1: 30 mg SC, N=4; cohort 2: 100 mg SC, N=6; cohort 3: 300 mg SC, N=6; cohort 4: 150 mg IV, N=6; cohort 5: 440 mg IV, N=6; cohort 6: 300 mg SC, 4 Japanese participants). A total of 9 healthy individuals received Placebo. **Study B7841009** was a Phase 1, open-label, randomised, single dose, 4-period, 2-sequence, full replicate crossover study in healthy adult male participants and compared the PK of a pre-filled syringe (used for the phase 3 trial) with a pre-filled pen. Both presentations are intended for marketing. Only PK data were collected during this bioequivalence study. While 38 participants (19 participants per sequence) were planned to be enrolled to have approximately 34 evaluable participants, only 22 participants were actually enrolled due to the occurrence of an event of deep vein thrombosis and pulmonary embolism leading to termination of the study. A total of 18 participants completed at least 1 period and contributed data for the calculation of PK parameters for PFS and PFP. A total of 11 participants completed all 4 periods and contributed data for the statistical analysis of the PK parameters.

The phase 1b/2 **Study B7841002** was a first-in-patients safety, efficacy and pharmacology study and recruited patients with haemophilia A or B, with or without inhibitors. The study consisted of 4 dose cohorts (cohort 1: non-inhibitors, 300 mg SC QW, N=7; cohort 2: non-inhibitors, 150 mg SC QW with a 300 mg loading dose,

N=6; cohort 3: non-inhibitors, 450 mg SC QW, N=6; cohort 4: inhibitors, 300 mg SC QW, N=7). The participants received weekly doses until up to Day 85, while blood samples were taken until Day 113.

The **extension Study B7841003** was an open-label long-term study on the safety, tolerability and efficacy of marstacimab during up to 365 days of treatment. The study included a total of 20 participants out of which 18 were rollovers from Study B7841002 and 2 were newly enrolled. Participants from Cohorts 1 and 4 of Study B7841002 kept their dose regimen of 300 mg SC QW, while all other participants (including the 2 newly enrolled participants and those who previously received 450 mg SC QW) received 150 mg SC QW with a loading dose of 300 mg SC.

The phase 1 Study **B7841010** investigated the PK/PD of a single SC dose of 300 mg marstacimab in Chinese adults with severe haemophilia A or B, with or without inhibitors (N=6, 5 with haemophilia A, 1 with haemophilia B).

The phase 3 **Study B7841005** was a one-way, cross-over, open-label, multi-centre study in adolescent and adult participants between ages 12 to <75 years with severe haemophilia A or moderately severe to severe haemophilia B (defined as FVIII activity <1%, or FIX activity \leq 2%, respectively) with or without inhibitors. The dossier only includes data from non-inhibitor patients (97 adult and 19 adolescent patients, 91 with haemophilia A and 25 with haemophilia B). All participants started treatment with an initial loading dose of 300 mg SC followed by 150 mg SC QW. If certain dose escalation criteria were met (patients weighing \geq 50 kg and experiencing 2 or more breakthrough bleeds), an increase of the weekly dose to 300 mg was allowed at any time after 6 months (D180 visit).

In **Study B7841007** (=extension of the phase 3 trial), blood samples for PK and PD assessments are only collected on a conditional basis as soon as possible for any participant who tested positive for both ADA and NAb during their participation in the study. This criterion was not met so far and therefore, no PK/PD data are available from the phase 3 extension study.

Investigated PD parameters and PK/PD sampling schedule

The main PD parameters investigated in the development program included plasma total TFPI, peak thrombin (via thrombin generation assay), prothrombin fragments 1+2 (PF 1+2), D-Dimer, and dilute prothrombin time (dPT).

Concentration of total TFPI in plasma (bound and free TFPI) is expected to increase after binding of marstacimab due to the longer half-life of the monoclonal antibody leading to delayed clearance of the complex. Therefore, total plasma TFPI levels reflect target binding.

The generation of thrombin (by cleavage of prothrombin) is an important step of the coagulation cascade. Thrombin is a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, which is able to form fibrin-based blood clots. The thrombin generation assay is an established method and considered as a suitable biomarker to investigate the procoagulant effect of marstacimab.

The commonly used safety laboratory parameters D-Dimer and PF 1+2 are both markers for activation of the coagulation system and considered relevant additional PD endpoints. The dilute prothrombin time (dPT) is an additional informative method to further characterise the effect of marstacimab on the coagulation status of the investigated subjects.

Overall, the choice of PD biomarkers is considered suitable to characterise the procoagulant effect of marstacimab. However, no data on the effect of marstacimab on free TFPI are available.

Efforts were made to develop and validate a free TFPI assay, however, free TFPI measurement from clinical samples was not possible. It was argued that the low nanomolar affinity of marstacimab with TFPI increases the risk of disassociation of the complex during analysis leading to unreliable free TFPI measurements. It should be noted that free TFPI measurements were performed for a very comparable development program (Chowdary *et al.* 2015, DOI: 10.1111/jth.12864). Lack of data showing the extent of inhibition of free TFPI is not optimal, considering that this constitutes the main mechanism of action of marstacimab. Such data were also considered important in earlier EMA scientific advice (Procedure No.: EMEA/H/SA/3363/2/2017/PA/II), especially because a flat dose regimen is foreseen. The Applicant was asked to further elaborate on the problems to obtain reliable free TFPI measurements. In the response, the Applicant pointed out that there are different isoforms and multiple binding partners of TFPI, which can have high binding affinity. The Applicant explained their attempts of developing a method to measure free TFPI. All strategies failed due to (1) sample dilution requirements and (2) reagent competition leading to dissociation of TFPI from the drug-target complex which would lead to an overestimation of free TFPI. The Applicant provided high-level data of two respective experiments, which is acknowledged. The Applicant further argued that marstacimab has a lower binding affinity for human TFPI, compared to other known TFPI inhibitors. A higher affinity for TFPI would significantly reduce the effect of sample dilution and reagent competition. Due to the lower nanomolar binding affinity of Marstacimab for TFPI and the large pool of TFPI bound with picomolar affinity to other endogenous proteins, the process of bioanalytical measurement, including both reagent binding and even minimal sample dilution disrupts TFPI-Marstacimab complex equilibrium thus releasing bound TFPI and resulting in inaccurate and overestimated free TFPI values. This justification is considered acceptable.

In the medical literature, under the term "free TFPI" they mean TFPI which is circulating (not membrane-bound) and not lipoprotein-bound. For a pharmacokinetics free TFPI means TFPI molecules with empty binding sites available to marstacimab binding. In fact, it seems that the POP-PK/PD report uses the term "free TFPI" in this sense. It was clarified that the "free TFPI" denotes all TFPI molecules with empty binding sites available to bind marstacimab. This definition is exact but strongly linked to this submission and differs from the standard terminology. In principle, this could be misleading, but not in this case because there are no references to the free TFPI molecules in the SmPC. Therefore, this is considered acceptable.

Out of the presented studies, the first-in-human Study B7841001 had the most extensive sampling schedule, with blood samples collected at 0 (predose), 1, 2 (IV cohort only), 4, 8 (IV cohort only), 12, 24, 48, 72 hours and on Days 7, 14, 21, 28, 35, 42, 56, 70 and 84 after administration of marstacimab. Such a long sampling period (up to Week 12) was necessary due to the long half-life of marstacimab. Depending on the dose, the half-life ranged from 33.3 to 98.35 hours after single dose administration in Study B7841001. Based on the population PK model, the mean effective steady state half-life (for weekly administrations) of marstacimab was estimated to be approximately 16 to 18 days for both adults and adolescents and across dose groups. Until Day 84, all measured PK/PD markers returned to baseline. During the first week, the sampling schedule was relatively dense. Overall, the sampling schedule of this first-in-human trial appears adequate.

The multiple dose studies had less frequent blood sampling schedules but in principle sufficient to determine the long-term effect on PD parameters.

Population PK and PK/PD modelling

The objectives of the population pharmacokinetic and pharmacodynamic modelling analyses were to develop an integrated, predictive population pharmacokinetic (PK) model for marstacimab plasma drug and total tissue factor pathway inhibitor (TFPI) concentrations, to identify potential covariates which impact marstacimab concentration levels, and to explore the relationship between free target (TFPI) and the key biomarker (peak thrombin) using pharmacokinetic-pharmacodynamic (PKPD) modelling.

There are two Population PK/PD reports. The first (report PMAR-EQDD-B784a-DP3-1021) uses data from the Phase 1 and Phase 2 studies, while the second (report PMAR-EQDD-B784a-DP3-1331) uses data from the Phase 3 study (study B7841005). Of note, an updated version of the second report was submitted with the responses to the D120 LoQ due to an input error. For the second report, a "full modelling approach" was used, i.e. all covariates considered relevant were included in the final model. Age (being an adolescent) as a factor was not included in the model because this variable strongly correlates with body weight. However, using the obtained model parameters, separate simulations were performed for the adolescent age group. Overall, from a methodological point of view, the POP-PK/PD model is properly validated, and the presentation of the POP-PK/PD report is in line with the requirements of the CHMP (Guideline On Reporting The Results Of Population Pharmacokinetic Analyses, CHMP/EWP/185990/06). The PK part of the combined POP PK/PD model is biologically meaningful: a target mediated drug disposition (TMDD) model with additional non-linear elimination of the drug was assumed. The model assumes that binding of the drug to the free receptor and dissociation of the drug-receptor complex are several orders of magnitude faster than the remaining system processes. This assumption allows the estimation of free (in pharmacokinetic sense) and bound concentrations of soluble TFPI (sTFPI).

Approximately half of the data points are derived from healthy volunteers. Although the percentage of BLQ samples is in total about 17%, it is still acceptable since this is mainly due to data from healthy volunteers and only about 5% of samples obtained from patients are BLQ.

The Applicant was questioned on regarding the fact that ADA positivity was only implemented as a baseline covariate (as opposed to a time-varying covariate) or the observation that the provided R-script detailing the simulations for the paediatric dose selection does not match the results provided. The Applicant tried to include ADA status as a time-varying variable in the model but either the estimates were unreliable (RSE 628%), or the model could not converge (all other parameters fixed). This was most likely also influenced by the limited data. If the model will be updated in the future, it is recommended to further investigate ADAs as the time-varying variable.

Overall, the provided updated population PK model seems to describe the observed data well for doses of 150 mg SC QW and lower and much better for the 300mg dose compared to the previously submitted model. However, the predicted values diverge from the observed values especially for higher concentrations and seem to underpredict higher concentrations. Although this is a shortcoming of the model, this might also be due to the limited data and could improve if further data might be integrated in the future.

The updated PK/PD model describes the data well also for higher concentrations.

Higher variability was noted in adolescent patients, but this might be due to the low number of patients in this age group. The Applicant did not discuss a potential effect of any other covariates nor were any explicitly tested in the PKPD model, which might be acceptable, if no effect is expected but no justification was provided. However, differences in free, total TFPI or peak thrombin might be explained by covariates also already included in the popPK model.

Results of the covariate analysis based on the popPK model are described further below (PK in special populations).

Bioanalytical assays

Fully validated assays were used for determination of marstacimab drug concentrations (PK), total plasma TFPI (PD) and detection of ADA and NAb. In principle, the presented bioanalytical methods were well described and

established. They were set up correctly and fully validated according to current EMA guidelines. Performance of the assays during clinical studies is considered acceptable.

The remaining PD parameters (thrombin generation, dPT, D-Dimer and prothrombin fragments 1+2) were measured using laboratory developed tests validated under CLIA requirements.

PK/PD in healthy adults

Following single dose SC administrations in **Study B7841001**, the marstacimab exposure increased in a more than proportional manner. For example, when comparing SC doses of 100 mg with 300 mg (3-fold dose increase, cohort 2 vs. cohort 3, N=6 each), the geometric mean Cmax increased from 1183 ng/mL to 16490 ng/mL (nearly 14-fold increase), and the geometric mean AUClast increased from 81890 ng*hr/mL to 3120000 ng*hr/mL (38-fold increase). Depending on the SC dose, the Tmax ranged from 48 to 108 hours and the t_{1/2} ranged from 33.3 to 98.35 hours. After single IV administrations (150 mg IV vs. 440 mg IV), the geometric mean Cmax increased in a roughly proportional manner (45640 ng/mL vs. 152800 ng/mL), while the geometric mean AUClast did also increase more than proportional (2346000 ng*hr/mL vs. 14290000 ng*hr/mL, 6-fold increase). It is assumed that marstacimab undergoes target-mediated drug disposition. Based on AUCinf, the bioavailability of SC dosing compared to the IV reference dose was 27%.

After single administrations of different dose levels in Study B7841001 in healthy adults, treatment related changes were observed for all PD endpoints and the response was roughly dose dependent. As expected, increases in total TFPI, peak thrombin, D-Dimer, and PF1+2 and shortening of TGA lag time and dilute prothrombin time were detected. The duration of the effect of the relevant dose levels did in principle support the intended weekly administrations of marstacimab.

Additional data on SC administrations of 300 mg (consisting of 2 injections of 150 mg each) are available from the bioequivalence **Study B7841009**, which compared the PK of a pre-filled pen (PFP) with a pre-filled syringe (PFS, used during the phase 3 trial). The descriptive analysis of the 18 participants who contributed data for the calculation of PK parameters for PFP and PFS showed comparable results for both administration devices (PFP vs PFS: geometric mean AUCinf [ng*hr/mL]: 2523000 vs. 2482000; geometric mean AUClast [ng*hr/mL]: 2018000 vs. 2015000; geometric mean Cmax [ng/mL]: 12550 vs. 12870; median Tmax [hr]: 72.00 vs. 72.00; arithmetic mean t_{1/2} [hr]: 61.29 ± 20.073 vs. 60.24 ± 13.687). As mentioned above, the study was terminated prematurely because of the occurrence of a deep vein thrombosis and pulmonary embolism. A statistical analysis using data from 11 participants who completed all 4 PK periods revealed test (PFP)/reference (PFS) ratios of adjusted geometric means for marstacimab AUClast and Cmax values of 107.5% (95.2%, 121.4%) and 104.1% (93.7%, 115.6%), respectively. The confidence intervals are within the pre-specified acceptance range of 80% - 125%. This result was confirmed by a sensitivity analysis of 15 participants who completed at least 2 periods (which means that they have received each treatment at least once) and also supported by the descriptive PK results of 18 participants who contributed PK data. While the early termination of the study is not optimal, one could argue that this led to a more challenging scenario for meeting the acceptance criteria due to the lower sample size.

PK/PD in patients

In the phase 1 single dose (300 mg SC) **Study B7841010** in Chinese haemophilia patients, the PK parameters of Tmax and Cmax were comparable with results from both studies in healthy adults (Study B7841001, Study B7841009) in cohorts using the same dose. The AUC and t_{1/2} values were higher in Chinese patients, but consistent with a small cohort of Japanese healthy adults (n=4) from Study B7841001 (detailed results for studies B7841010, B7841001 and B7841009 are shown in the results section). In line with the single dose trial in healthy adults (B7841001), changes in PD parameters (increased plasma total TFPI, PF 1+2, D-Dimer, peak

thrombin, and TGA endogenous thrombin generation potential, shortening of dPT and TGA lag time) were maintained for more than a week. For most of these PD parameters, the maximum effect was observed within the first week, except for total plasma TFPI and D-Dimer, which peaked later (during week 2 or 3, respectively).

In the phase 1b/2 **Study B7841002**, weekly administration of marstacimab led to an increasing plasma concentration up to the Day 29 visit. The plasma concentrations at the following visits (Day 57, Day 85) were lower or comparable, suggesting that a steady state may have been reached. This should however be interpreted with caution due to the small sample size and reference is made to the discussion of the longer-term data of the phase 3 trial B7841005 were accumulation of marstacimab was noted for the weekly dose of 300 mg. At Day 29, PK parameters such as AUCtau, Cmax, and Cmin seemed to be dose-dependent, with the highest values observed for the 450 mg SC QW group and the lowest values for the 150 mg SC QW (+300 mg SC loading dose) group. Importantly, the more than proportional increase in PK parameters such as Cmax and AUC (as described for the first-in-human single dose study in healthy adults) was not observed during the multiple dose study in haemophilia patients, at least not to the same extent. It should however be noted that the lower dose levels of Study B7841001 (30 mg SC, 100 mg SC) were not investigated during Study B7841002 and that the 150 mg SC QW cohort received a loading dose of 300 mg. A possible explanation for the roughly dose-dependent increase in PK parameters could be that the linear elimination likely dominates at the dose levels (and plasma concentrations) investigated during the multiple dose trials due to a saturated drug target (TMDD).

While Study B7841002 suggested that steady state concentration of marstacimab might have been reached until Day 85, the PK data of the **extension Study B7841003** do not allow a clear conclusion on this aspect for the higher dose regimen (300 mg SC QW). Among the participants who received weekly doses of 300 mg (participants with or without inhibitors combined) throughout the study, the mean plasma concentrations of marstacimab were higher at later time points compared to Day 85 (Day 85: 41720 ng/mL, N=10; Day 169:

patients, the plasma concentrations of marstacimab did continue to increase until D365, while the levels were stable or decreasing for inhibitor patients. The interpretability of these one-year PK data seems limited due to the small number of participants in the different dose cohorts of this study.

During the multiple dose Study B7841002 and its extension Study B7841003, the effects on PD parameters tended to increase until either Day 85 (increased PF1+2) or Day 169 (total TFPI, increased peak thrombin, shortened TGA lag time, increased endogenous thrombin generation potential) and remained roughly comparable until the end of the extension study.

In the **phase 3 Study B7841005**, 102 participants (85 adults, 17 adolescents) received a weekly dose of 150 mg SC marstacimab (after an initial loading dose of 300 mg) throughout the whole study duration of one year. For 14 participants (12 adults, 2 adolescents), the weekly dose was escalated to 300 mg SC after the D180 visit.

Among the 102 participants who remained on the 150 mg SC WQ dose regimen throughout the study, the marstacimab plasma concentration seemingly reached a steady state around Day 60. Adolescents reached higher mean plasma concentrations (roughly around 21000-27000 ng/mL, SD ~ 12000-18000) than adults (roughly around 12000-14000 ng/mL, SD ~ 10000-13000) throughout the visits at Day 60, Day 120, Day 180, Day 240, Day 300 and Day 360. A higher plasma concentration in adolescents was predicted by the population PK model. The variability of these PK measurements was high, as shown by the standard deviation values. In the phase 3 study, the coefficients of variation were approximately between 40% - 85% in adolescents and between 62% - 92% in adults. In the CSR it is argued that the variability was likely caused by differences in sampling time points. In order to support this hypothesis, the Applicant was asked to provide an overview with

more details on the variability of the sampling time points. The Applicant clarified that blood samples were collected at any time during the clinical visit, regardless of the time of dose administration. While recommendation was made in the protocol that the PK sample be collected prior to dose administration, this was not mandatory. Approximately 50% of samples were obtained pre-dose (at around 6 days post dose or later), while 50% of samples were obtained anytime between 1 – 5 days post dose. Besides patient weight, variable soluble and cell surface levels of TFPI may also contribute to variability.

Based on how the data were presented in the initial submission, it seemed that marstacimab and TFPI were continuously increasing in those 14 participants who had a dose escalation to 300 mg SC QW during the phase 3 Study. In addition, the population PK/PD model did not adequately describe the data observed for the 300 mg SC QW dosing. This issue was raised as a major objection in the D120 LoQ since accumulation of marstacimab and a potential risk for thrombosis could not be excluded. A more detailed presentation of the data in dose-escalated participants was requested.

In the response to this major objection, the Applicant provided detailed tables and figures describing all data points (marstacimab concentration, total TFPI) in participants who switched to the higher dose regimen, an update of the population PK/PD model (correcting an input error), and updated discussions on the safety and efficacy of marstacimab based on a later data cut-off of the extension study B7841007.

Among the 14 participants who received 300 mg SC QW during the phase 3 Study B7841005, 6 participants had 3 PK data points (**marstacimab concentration** in plasma) after dose escalation, covering a period of ~120 days between the sampling time points. Importantly, there was no sign of accumulation in these participants. For the remaining 8 participants, only one or two PK data points were available, because they switched their dose at later time points during the study. The measured marstacimab concentrations were within the observed range of the overall study population. The mean plasma concentration in all participants who had a dose escalation did only slightly increase between D300 and D360, while the median concentrations remained stable. Based on the provided data, it seems that the data in the initially provided Figure above were biased due to different time points of dose escalations, leading to the wrong impression of a continued increase of marstacimab in plasma over time. This could not be assessed in the previous round based on how the data were presented in the initial submission. The same observation was made for **total TFPI**.

In addition, the Applicant provided an amended population PK and PK/PD model, including an updated report. The Applicant claimed that this was made to correct an error in the dosing record inputs for the 300 mg dose (150 mg input instead of 300 mg) in Study B7841005 in the NONMEM dataset used for population PK modelling. The data cutoff remained the same as previously (ie, all data up to Day 300 was included). The modelling predictions (marstacimab concentration, total TFPI) for the 300 mg SC QW dose now show better agreement with the observed data. The amended model is now considered more suitable for use with the higher dose (300 mg SC QW).

Updated safety & efficacy data from a more recent data cut (09 Oct 2023 vs. 10 Mar 2023 in the previous submission) from the extension Study B7841007 were provided. Additional participants had a dose escalation during the extension study. At the new data cut-off, there were a total of 23 participants who have been dose escalated from 150 mg marstacimab to 300 mg marstacimab, either in Study B7841005 or Study B7841007 (13 HA participants, 10 HB participants). No PK/PD data are collected during the ongoing extension study. There were no SAEs in dose escalated participants and importantly also no thromboembolic events in any haemophilia patient treated with marstacimab (regardless of the dose level). While this is reassuring, the very small safety database needs to be considered. The Applicant provided additional efficacy data based on the later data cut-off (09 Oct 2023) and there was no sign of reduced efficacy in this population.

Based on the more detailed data, the major concern regarding a potential accumulation of marstacimab (and total TFPI) was considered resolved. The presented data support the proposed dose regimen, which allows a dose escalation to 300 mg SC QW when control of bleeding events is judged to be inadequate by the healthcare professional.

For patients who remained on the 150 mg SC QW dose level, the **peak thrombin** values seemed to have reached a steady state at Day 60, with median values ranging from 63 – 66 nM in adults (N=85) compared to 41 - 54 nM in adolescents (N=17). Paradoxically, for the 14 participants who underwent dose escalation to 300 mg SC QW during the trial, the median peak thrombin levels started to continuously decrease over time after every subsequent visit. The median peak thrombin levels decreased from >70 nM at Day 180 to around 30 nM at Day 360. This is unexpected and contradicts the results of a previous smaller study (Study B7841003, Figure 5 in the Clinical AR). Potential reasons and consequences of this unexpected observation and whether it can be excluded that this might have been caused by some form of drug tolerance or by development of antibodies against marstacimab were discussed. Only 3 of the 14 dose-escalated participants contributed to the median peak thrombin. In addition, these 3 data points were incorrectly assigned as post-dose data at this time point and that the actual number contributing data at the D180 time point for 300 mg SC QW is 0. However, an updated figure (not included in this report), which only includes data starting from D240, still shows a downward trend for median TGA peak values that is similar to the trend shown (from ~55 nM to ~30 nM). The Applicant argued that efficacy was maintained during the extension of the phase 3 study, that the peak thrombin values were stable over time during the phase 2 study, that other PD biomarkers remained stable during phase 3, that the “n” in the concerned population of dose-escalated participants was small, and that the variability of PD measurements was generally high. For the few concerned participants who developed ADA, no meaningful impact on peak thrombin was noted. The totality of the provided arguments was considered reassuring.

Overall, the median thrombin peak levels remained within a physiological range throughout the study. A summary on how often the thrombin peak values were elevated above the upper limit of normal (by subject incidence and individual occurrences), whether the values returned to normal until the end of the study and a summary and discussion on the PD parameters of D-Dimer and PF 1+2 were requested. These data should be discussed with respect to potential safety risks. It was clarified that ~50% of the blood samples were collected pre-dose (Day 6 after last administration of Hympavzi), whereas the remaining samples were obtained anytime between 1 – 5 days post dose (multiple dose Tmax = 23 – 59 hours). For contextualization of the analyses of the PD marker (peak thrombin, D-Dimer, PF1+2) values measured during the phase 3 trial, the Applicant provided not only physiological ranges for these markers from the literature, but also an analysis of pre-dose (baseline, n=41 participants) and post-dose (n=27 participants) values of the healthy volunteers recruited for the phase 1 trial B7841001.

Three out of 116 participants of the phase 3 trial had peak thrombin values above 176 nM, which is the 97.5th percentile for normal range in healthy participants of the phase 1 study. The elevated levels were only transient and returned to normal. For one of these 3 cases, sample collection occurred within 2 days of a bleed.

In the phase 3 study, 33 out of 116 haemophilia participants had at least 1 D-Dimer value > 0.52 µg/mL, the 97.5th percentile for normal range in healthy participants. The maximum observed post-dose value in the haemophilia population was 1.9 µg/mL (97.5th percentile = 0.81 µg/mL), in comparison to a maximum post-dose value of 6.1 ug/mL in the healthy population (97.5th percentile = 2.5 ug/mL). Out of the 33 participants, 20 participants had D-Dimer > 0.52 µg/mL at more than 1 timepoint (range = 2 – 8 timepoints) after which values returned to normal. Ten (10) participants had D-Dimer > 0.52 µg/mL at Day 360, i.e. at the end of study.

Nearly all (112 out of 116) haemophilia participants of the phase 3 Study had PF1+2 values > 181 pmol/L, which is the 97.5th percentile for normal range in healthy participants. Values greater than 181 pmol/L were seen at 2 or more time points (between 2 – 9 time points) post dose. The maximum value seen in haemophilia participants was 12801 pmol/L (at 1 time point in 2 participants before end of study). The 97.5th percentile for post-dose PF1+2 was 1290 pmol/L in haemophilia participants in comparison to the 97.5th percentile of 961 pmol/L in healthy participants.

The applied exact thresholds for peak thrombin, D-Dimer and PF1+2 may be debatable. It is reassuring that no thromboembolic events occurred in any of the clinical trials which recruited haemophilia patients, including the latest data cut-off of the extension study B7841007. In order to inform the prescriber, a statement was included in section 5.1 of the SmPC describing that potentially elevated values (above the physiological range) may occur for D-Dimer or PF1+2.

For the PD parameters of **PF 1+2** and **D-dimers**, steady state was also reached at Day 60. The median values for absolute PF 1+2 ranged from 492 – 579 pmol/L in adults (N = 85) in comparison to 557 – 874 pmol/L in adolescents (N = 17). The median values for absolute D-dimer were around 0.3 µg/mL in adults (N = 85) in comparison to roughly 0.25 – 0.45 µg/mL (with a decreasing trend over time) in adolescents (N = 17). In contrast to peak thrombin, the PF 1+2 and D-dimer levels remained on comparable levels after dose escalation to 300 mg SC QW.

Immunogenicity

In the pooled Phase 2 studies (Studies B7841002/B7841003), the total incidence of ADA was 10.7%. None of the participants tested positive for marstacimab NAb.

In the pooled Phase 3 studies (Study B7841005/B7841007), the total incidence of ADA was 19.8% (23/116 participants). Overall, ADA titres were low, transient in the majority of the participants and resolved in all but one (i.e., 22/23 = 95.7%) ADA-positive participant by the end of the parent study. The NAb incidence was 5.2%, all NAb were transient in nature and no participants were NAb positive at end of the parent study or during the OLE study.

The Applicant summarised PK/PD data by ADA status. The data from the phase 1/2 trial do not allow any conclusions due to the small number of participants in relevant dose groups. For the phase 3 study, upon request, the Applicant provided detailed tables including descriptive statistics for plasma marstacimab and PD parameters by ADA status. The mean marstacimab concentrations were lower in ADA positive participants compared to negative participants throughout all clinical visits. At Day 360, mean marstacimab concentration was 10550 ng/mL in ADA positive participants, and 15570 ng/mL in ADA negative participants (median 8340 ng/mL vs. 12300 ng/mL). The same pattern was seen for total TFPI in plasma with lower mean and median values observed in ADA negative participants compared to ADA positive participants throughout all visits (e.g., Day 360 mean TFPI values; ADA+: 258.4 ng/mL; ADA-: 322.2 ng/mL). A comparable but less consistent trend was seen for PF1+2. ADA status did not seem to influence TGA peak values and Dilute Prothrombin Time (sec). Even if an impact on efficacy is not necessarily expected based on data presented, information about the observed influence of ADA on PK was included in the SmPC.

PK in special populations

Based on the population PK analysis, haemophilia type did not seem to significantly influence the PK of marstacimab. Effect of age was not included as a covariate in the model because of the young age of the haemophilia population with median age of 31 years (range: 13 – 66 years) in the studies. Lack of data in

elderly is reflected in the SmPC. The data on ethnic factors is very limited. After adjusting for weight, marstacimab clearance was estimated to be approximately 31.9% higher in Asian participants.

Some individuals with mild renal (N=22; eGFR of 60-89 mL/min/1.73 m²) or hepatic (N = 15, total bilirubin > ULN, AST > ULN) impairment were recruited. Population analysis of the effect of renal impairment on marstacimab CL showed a 16.8% lower CL with mild renal impairment (95% CI: -34% to 12.1%). No clinically significant impact is expected in these patients. The lack of data in patients with moderate or severe forms of renal/hepatic impairment is reflected in the SmPC.

Based on population PK analysis, weight was the most important covariate which seemed to influence the PK of marstacimab. Lower weight seems to cause lower clearance (and higher exposure). For example, differences in clearance between adults and adolescents were noted, with lower clearance (~32%) and higher median marstacimab plasma concentrations reported for adolescents. After weight-adjustment, the difference in clearance was only ~3%. This is reflected in section 5.2 of the SmPC.

The Applicant was asked to discuss and justify why no dose adjustment is recommended for obese and underweight subjects in section 4.2 of the SmPC. Simulated steady-state individual post-hoc PK exposure using the amended population PK model and simulations for peak thrombin using the same PK/PD model were performed. Based on limited data from **obese participants (n=11)**, the simulated marstacimab exposure levels were lower compared to healthy weight or overweight participants. However, the simulated TGA peak values were comparable between the groups, with a trend for slightly higher values in these few obese participants. In contrast, the simulated exposure was higher in **underweight participants (n=24)** compared to healthy weight or overweight participants. There seemed to be a trend for slightly lower simulated TGA peak values compared to the other weight groups. No inconsistencies or outliers were detected with respect to annualised bleeding rates in obese participants. In underweight participants, there were 3 participants with an ABR above 10, but the rate of outliers was comparable to the healthy weight or overweight participants.

No thromboembolic events were reported, but the sample size is too low to make any firm conclusions based on safety data. The absence of a narrow therapeutic window is acknowledged.

Based on the provided PK/PD and efficacy data, it can be agreed that there seems to be no need for dose adjustment of the 150 mg SC QW dose in obese or underweight patients. The Applicant has adequately discussed the effects of the 300 mg dose on PK, safety and efficacy in underweight subjects with a view to justify why there is no need for dose adjustment in this setting, considering that these individuals seem to have notably higher simulated mean steady state marstacimab concentrations (but lower peak thrombin levels) with the 150 mg SC QW dose, compared to healthy weight participants. Estimated Cmax values for marstacimab as well as estimated TGA values overlap between normal weight/overweight subjects and underweight subjects who have been escalated to the higher dose. No safety signals were observed in patients who were treated with 300 mg, irrespective of bodyweight. As dose escalation is permitted only for those subjects with a minimum bodyweight of 50 kg and only if the observed bleeding control is not deemed sufficient, no additional warnings are considered necessary in the SmPC.

2.6.4. Conclusions on clinical pharmacology

The methodology and conduct of the clinical pharmacology studies are acceptable. Clinical pharmacology parameters and pharmacodynamics markers have been adequately studied and relevant information has been reflected in SmPC sections 4.2, 4.4 and 5.2. After weekly SC administration of 150 mg study drug (after a 300 mg loading dose) in the phase 3 trial, the concentrations of marstacimab and total TFPI in plasma reached a

steady state at the Day 60 visit. The PD biomarker of peak thrombin increased to physiological values and the measured downstream biomarkers for coagulation (PF 1+2, D-Dimer) showed consistent response throughout the study. The proposed dose regimen in section 4.2 of the SmPC includes the option of a dose escalation to 300 mg SC QW in patients with inadequate control of bleeding events, as judged by the healthcare professional. Although only limited data are available for this dose escalation setting, the Applicant provided sufficient reassurance that there are no signs for accumulation of marstacimab. There were no thromboembolic events in haemophilia patients in any of the clinical studies.

Several PD markers were measured during the clinical program. The relationship between the levels of these biomarkers and the primary efficacy parameter (ABR) has not been investigated. Measuring TFPI activity would have been the most straightforward way to connect pharmacodynamics and clinical efficacy. The Applicant argued that all strategies of developing a method to measure free TFPI failed because of (1) sample dilution requirements and (2) reagent competition leading to dissociation of TFPI from the drug-target complex due to the relatively low binding affinity of marstacimab to TFPI compared to other known binding partners, which would lead to an overestimation of free TFPI.

2.6.5. Clinical efficacy

Clinical efficacy data from 4 studies are provided in the MAA for Hympavzi, which include a single pivotal Phase 3 study and its Phase 3 OLE study, as well as one Phase 1b/2 study and its Phase 2 OLE.

The single pivotal study B7841005 investigating both non-inhibitor and inhibitor cohorts is currently ongoing, however efficacy data from the completed non-inhibitor cohort are available for review. The Phase 3 OLE study B7841007 is ongoing with an interim analysis for the non-inhibitor cohort provided with a cut-off date of 10 March 2023. Further, supportive efficacy data are provided from the completed studies B7841002 (Phase 1b/2) and B7841003 (Phase 2 OLE).

The indication applied for with this MAA is restricted to the non-inhibitor patient population only.

Data provided from patients who were previously on routine prophylaxis during OP are considered the pivotal evidence for this MAA. Comparison of marstacimab prophylactic treatment and previous on-demand treatment is considered to be of decreased regulatory importance and is viewed as supportive evidence.

Table 14: Clinical efficacy studies included in the marstacimab MAA

Study	Description	Population	N (Active/ Placebo)	Dose(s) / Frequency	Duration	Age (Years)	Study Status
Phase 1b/2 and Phase 3 Studies Contributing Efficacy and Safety Data for the Proposed Indication							
B7841002	Phase 1b/2 multiple dose proof of concept	Severe hemophilia A & B	26/0 Non-inhibitor cohort: 19 Inhibitor cohort: 7	150, 300, 450 mg / QW	3 months	18 to ≤65	Completed
B7841003	Phase 2 OLE	Severe hemophilia 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
B7841005	Phase 3 Pivotal non-inhibitor cohort	Severe hemophilia A & moderately severe to severe hemophilia B	Non-inhibitor cohort: 116/0	150 mg / QW ^a	12 months	12 to <75	Non-inhibitor cohort: completed Inhibitor cohort: ongoing
B7841007	Phase 3 OLE of Study B7841005	Severe hemophilia A & moderately severe to severe hemophilia B	Non-inhibitor cohort: 87/0	150 mg / QW ^a	Up to approximately 16 months at time of submission (in addition to 12 months exposure in Study B7841005)	12 to <75	Non-inhibitor and inhibitor cohorts: ongoing

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

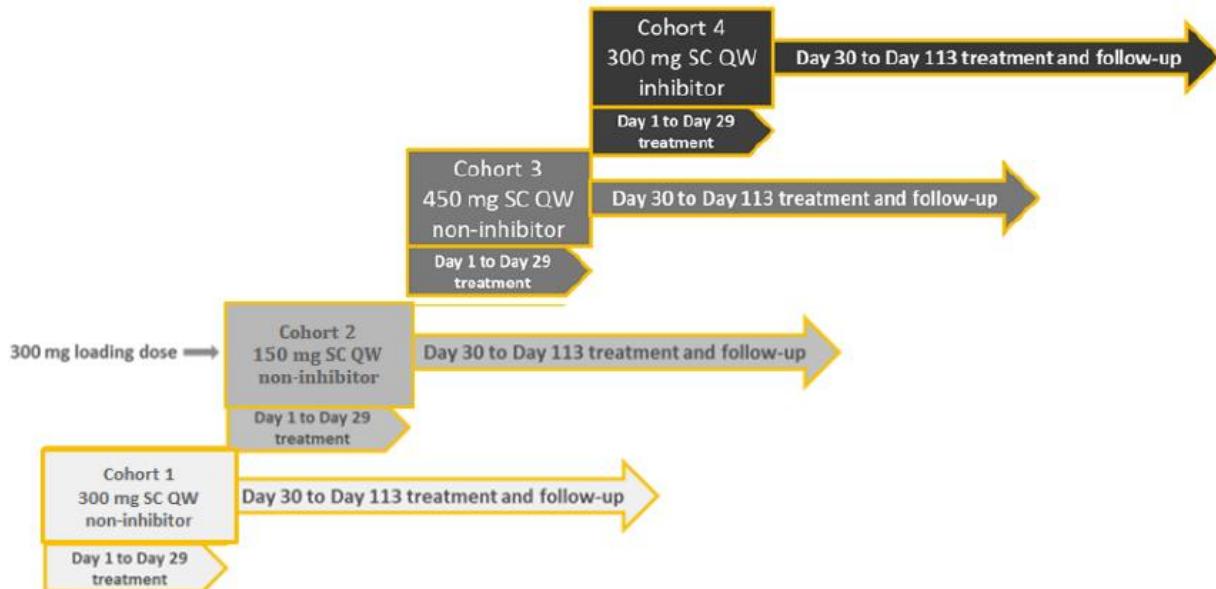
2.6.5.1. Dose response study(ies)

B7841002: Phase 1b/2 Study

Study B7841002 was a Phase 1b/2, open-label, multiple ascending dose clinical study in male participants with severe haemophilia A or B, with or without inhibitors.

The dose progression scheme and treatment duration of the study is described in Figure below.

Figure 21: dose progression scheme



Twenty-seven (27) participants were enrolled at 9 study sites. Subcutaneous (SC) multiple dose cohorts were enrolled starting at the 300 mg SC dose. Intravenous (IV) routes of administration were not evaluated in the study. Participants were enrolled and assigned to the study treatments in four cohorts: Cohort 1 (noninhibitor, n = 8) with 300 mg weekly s.c. dosing, Cohort 2 (non-inhibitor, n = 6) with 300 mg loading dose followed by 150 mg weekly s.c. dosing, Cohort 3 (non-inhibitor, n = 6) with 450 mg weekly s.c. dosing. The inhibitor cohort (Cohort 4) was treated with 300 mg weekly s.c. dosing, which was assessed as safe and welltolerated in participants without inhibitors before treatment of inhibitor patients was initiated.

Cohorts were followed for at least 29 days. If available safety, tolerability and pharmacokinetic (PK) data through Day 29 were permissive for dose escalation, a cohort at a higher dose level was to be opened for enrollment. Alternatively, a cohort at a lower dose level was to be opened if data were supportive. In addition, if the dose level under review was safe and well tolerated through Day 29, treatment was to continue for the participants in that respective cohort during the subsequent 2 months (Day 30 to Day 85).

Eligible participants were patients with severe haemophilia A or B (FVIII or FIX activity $\leq 1\%$) with ondemand treatment regimen, including those with inhibitors to FVIII or FIX.

For efficacy evaluation, frequency and annualised rate of bleeding episodes from day 1 to day 85 were investigated as the key secondary endpoint of the study. Information on bleeding episodes over the 6 months prior to the study were collected at screening, information on new bleeding episodes after screening were collected continuously to day 113 (FU/EOS). Additionally, a historical on-demand group was constructed using data from the following internal Pfizer studies: ReFacto AF 3082B2-4432 (B1831004), BeneFIX B1821010, and BeneFIX 3090A1-400 (B1821004).

Results

Subject Disposition and Demography:

38 individuals were screened, of which, 11 individuals failed at screening. Among the 27 participants who met the eligibility criteria and were assigned to the study treatment, 26 (96.3%) participants were treated with PF-06741086, and 1 (3.7%) participant assigned to the PF-06741086 300 mg SC QW non-inhibitor dose cohort was not treated due to consent withdrawal prior to dosing on Day 1.

Among 26 participants treated with PF-06741086, 24 (92.3%) participants completed the study, and 2 (7.7%) participants discontinued from study due to AEs. One (1) participant from the PF-06741086 300 mg SC loading + 150 mg SC QW non-inhibitor dose cohort discontinued from study due to a Grade 2 non-serious AE of hypertension, which was determined to be treatment related by the investigator. 1 participant from the PF-06741086 300 mg SC QW inhibitor dose cohort discontinued from study due to a Grade 3 non-serious AE of decreased blood fibrinogen, which was determined to be treatment related by the investigator.

All 26 participants were male. The majority of participants (19/26, 73.1%) were in the 18-44 age range. All 26 participants were of White (14/26, 53.8%) or Black/African American race (12/26, 46.2%). The median weight ranged from 61.60 kg (PF-06741086 300 mg SC loading + 150 mg SC QW non-inhibitor dose cohort) to 82.85 kg (PF-06741086 450 mg SC QW non-inhibitor dose cohort) and individual values ranged from 50.2 to 96.0 kg. The median body mass index (BMI) ranged from 21.26 kg/m² (PF-06741086 300 mg SC loading + 150 mg SC QW non-inhibitor dose cohort) to 26.30 kg/m² (PF-06741086 450 mg SC QW non-inhibitor dose cohort) and individual values ranged from 17.8 to 30.4 kg/m².

Among 26 treated participants, 23 (88.5%) participants had haemophilia A and 3 (11.5%) participants had haemophilia B. All 7 (100%) participants in the PF-06741086 300 mg SC QW inhibitor dose cohort had haemophilia A and inhibitors to FVIII.

Efficacy results

A descriptive summary of ABR data is presented by study phase in below Table.

Table 15: description summary of annualised bleeding rate by dose cohort -PPAS

Study Phase	Summary Statistics	PF-06741086 300 mg SC QW Non-Inhibitor (N = 6)	PF-06741086 300 mg SC Loading + 150 mg SC QW Non-Inhibitor (N = 6)	PF-06741086 450 mg SC QW Non-Inhibitor (N = 6)	PF-06741086 300 mg SC QW Inhibitor (N = 6)	Historical On Demand Group (N = 65)	Overall - PF-06741086 300 mg SC (N = 12)	Total (N = 24)
Pre-Treatment ^a	n	6	6	6	6	0	12	24
	Mean	23.00	14.67	20.33	17.33	-	20.17	18.83
	SD	7.457	1.633	10.838	3.011	-	6.177	7.100
	Median	24.00	15.00	17.00	18.00	-	19.00	17.00
	Min	12.0	12.0	12.0	12.0	-	12.0	12.0
	Max	30.0	16.0	42.0	20.0	-	30.0	42.0
On-Study	n	6	6	6	6	65	12	24
	Mean	4.22	1.62	4.17	0.65	27.56	2.43	2.67
	SD	3.799	2.533	6.467	1.603	17.028	3.345	4.092
	Median	4.15	0.00	0.00	0.00	22.56	0.00	0.00
	Min	0.0	0.0	0.0	0.0	0.5	0.0	0.0
	Max	8.5	5.5	12.6	3.9	67.6	8.5	12.6

The historical On Demand group was constructed using the following internal Pfizer studies: ReFacto AF 3082B2-4432 (B1831004), BeneFIX B1821010, and BeneFIX 3090A1-400 (B1821002).

The overall PF-06741086 300 mg SC group combined subjects from both the PF-06741086 300 mg SC QW non-inhibitor and inhibitor dose cohorts.

One (1) subject from the PF-06741086 300 mg SC QW non-inhibitor dose cohort was excluded from the PPAS due to a treatment interruption >30 days caused by an AE of appendicitis.

The dose of 1 subject was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the subject was analyzed in the PF-06741086 450 mg SC QW non-inhibitor dose cohort.

a. Summarized the data up to 6 months prior to study enrollment.

Table 14.2.1.1.1 is for Pfizer internal use.

The comparisons for ABR between the PF-06741086 dose cohorts and the historical On Demand group using a negative binomial model are provided in the table below. There was a statistically significant reduction in ABR in the pooled PF-06741086 dose cohorts (24 participants) versus that in the historical On Demand group (ratio [test/reference] = 0.10, 80% CI = 0.07 to 0.14, p <0.0001). The reduction in ABR remained statistically significant in each PF-06741086 dose cohort versus that in the historical On Demand group.

Table 16: statistical summary of annualised bleeding rate versus historical on demand group based on negative binomial model – PPAS

Comparison (Test vs. Reference)	Mean (80% CI)		Ratio (Test/Reference)	80% CI	P Value
	Test	Reference			
PF-06741086 300 mg SC QW Non-Inhibitor vs. Historical On Demand Group	4.20 (2.23, 7.89)	27.63 (24.67, 30.93)	0.15	(0.08, 0.29)	0.0002
PF-06741086 300 mg SC Loading + 150 mg SC QW Non-Inhibitor vs. Historical On Demand Group	1.47 (0.56, 3.90)	27.62 (24.66, 30.95)	0.05	(0.02, 0.14)	0.0001
PF-06741086 450 mg SC QW Non-Inhibitor vs. Historical On Demand Group	4.17 (2.21, 7.87)	27.62 (24.63, 30.99)	0.15	(0.08, 0.29)	0.0002
PF-06741086 300 mg SC QW Inhibitor vs. Historical On Demand Group	0.72 (0.19, 2.73)	27.62 (24.65, 30.95)	0.03	(0.01, 0.10)	0.0005
Overall - PF-06741086 300 mg SC vs. Historical On Demand Group	2.49 (1.44, 4.29)	27.62 (24.66, 30.94)	0.09	(0.05, 0.16)	<0.0001
Total vs. Historical On Demand Group	2.67 (1.83, 3.89)	27.62 (24.63, 30.98)	0.10	(0.07, 0.14)	<0.0001

The historical On Demand group was constructed using the following internal Pfizer studies: ReFacto AF 3082B2-4432 (B1831004), BeneFIX B1821010, and BeneFIX 3090A1-400 (B1821002).
The overall PF-06741086 300 mg SC group combined subjects from both the PF-06741086 300 mg SC QW non-inhibitor and inhibitor dose cohorts.
One (1) subject from the PF-06741086 300 mg SC QW non-inhibitor dose cohort was excluded from the PPAS due to a treatment interruption >30 days caused by an AE of appendicitis.
The dose of 1 subject was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the subject was analyzed in the PF-06741086 450 mg SC QW non-inhibitor dose cohort.
Table 14.2.3.1 is for Pfizer internal use.

The comparisons between on-study ABR and pre-treatment ABR in the PF-06741086 dose cohorts using a negative binomial model are provided below. There was a statistically significant reduction in ABR in the on-study phase versus that in the pre-treatment phase in the pooled PF-06741086 dose cohorts (ratio [on-study/pre-treatment] = 0.14, 80% CI = 0.09 to 0.22, p <0.0001). The reduction in ABR in the on-study phase versus that in the pre-treatment phase remained statistically significant in each PF-06741086 dose cohort.

Table 17: Statistical summary of on-study versus pre-treatment annualised bleeding rate based on negative binomial model - PPAS

Treatment Group	Comparison (Test vs. Reference)	Mean (80% CI)		Ratio (Test/Reference)	80% CI	P Value
		Test	Reference			
PF-06741086 300 mg SC QW Non-Inhibitor	On-Study vs. Pre-Treatment	4.19 (2.72, 6.45)	23.00 (19.70, 26.85)	0.18	(0.11, 0.31)	<0.0001
PF-06741086 300 mg SC Loading + 150 mg SC QW Non-Inhibitor	On-Study vs. Pre-Treatment	1.45 (0.67, 3.15)	14.67 (13.91, 15.47)	0.10	(0.04, 0.22)	0.0002
PF-06741086 450 mg SC QW Non-Inhibitor	On-Study vs. Pre-Treatment	4.17 (1.99, 8.74)	20.33 (15.76, 26.23)	0.20	(0.09, 0.47)	0.0154
PF-06741086 300 mg SC QW Inhibitor	On-Study vs. Pre-Treatment	0.73 (0.23, 2.29)	17.33 (15.95, 18.83)	0.04	(0.01, 0.14)	0.0005
Overall - PF-06741086 300 mg SC	On-Study vs. Pre-Treatment	2.49 (1.55, 4.01)	20.17 (18.09, 22.48)	0.12	(0.08, 0.20)	<0.0001
Total	On-Study vs. Pre-Treatment	2.67 (1.79, 3.97)	18.83 (17.10, 20.74)	0.14	(0.09, 0.22)	<0.0001

The overall PF-06741086 300 mg SC group combined subjects from both the PF-06741086 300 mg SC QW non-inhibitor and inhibitor dose cohorts.
One (1) subject from the PF-06741086 300 mg SC QW non-inhibitor dose cohort was excluded from the PPAS due to a treatment interruption >30 days caused by an AE of appendicitis.
The dose of 1 subject was modified from 450 mg to 300 mg due to multiple severe injection site reactions; the subject was analyzed in the PF-06741086 450 mg SC QW non-inhibitor dose cohort.

2.6.5.2. Main study

Pivotal Phase 3 study B7841005

Methods

Study B7841005 is an ongoing, one-way, cross-over, open-label, multi-centre study planned for approximately 145 adolescent and adult participants between 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 inhibitor, with approximately 20% of participants as adolescents (ages between 12 to <18 years old). Study B7841005 originally allowed for enrolment of participants with severe haemophilia A and severe haemophilia B. Protocol Amendment 6 added the inclusion of participants with moderately severe haemophilia B. In the non-inhibitor cohort, only severe haemophilia B participants have enrolled. The non-inhibitor cohort of this study is complete, whereas the inhibitor cohort is ongoing.

This study compared 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 were eligible for dose escalation to 300 mg SC QW.

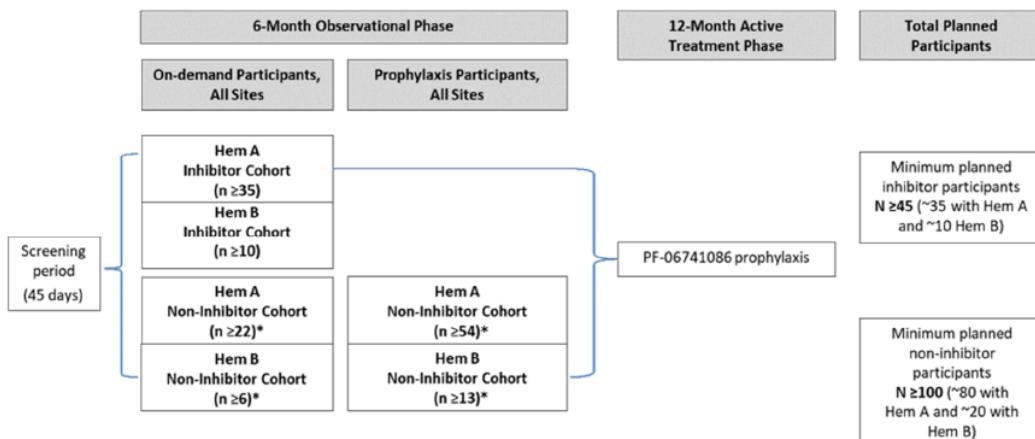
Treatment during the 6-month OP consisted of the following:

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.

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.

Figure 22: Study schema



- **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

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 Enrollment. 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 Enrollment.
- Participants who are enrolled into the **Non-Inhibitor Cohort** must also meet the following criteria:
 - No detectable or documented history of inhibitors (≥0.6 BU/mL or greater than the upper limit of normal [ULN] for the testing laboratory) against FVIII or FIX prior to enrollment (Baseline of Observational Phase).
 - Participants receiving routine prophylaxis (defined as treatment by IV injection of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement, have demonstrated at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrollment, and willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the Observational Phase.

(OR)

- Participants with on-demand treatment regimen with ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months period prior to Enrollment 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.

Sex

- Male

Informed Consent

- Participant or legally authorised representative, or participant's caregiver capable of giving signed informed consent (or minor assent, when applicable) 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 hemostatic 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, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention) is acceptable if the participant otherwise meets entry criteria
 - Serum albumin less than the lower limit of normal (LLN).
 - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m².
- Abnormal hematology 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 (eg, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), non-coagulation non-factor replacement therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of haemophilia.
 - Participants with inhibitors who are being treated using a prophylaxis treatment regimen with a bypass agent will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
 - Participants who have previously received non-factor-based haemophilia therapy (eg, fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
- Regular, concomitant therapy with immunomodulatory drugs (eg, IV immunoglobulin [IVIG], and routine systemic corticosteroids, rituximab).
- Ongoing or planned use of immune tolerance induction during the Observational Phase or Active Treatment Phase, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the Active Treatment Phase.

Prior/Concurrent Clinical Study Experience

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

Diagnostic assessments

- CD4 cell count \leq 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 Exclusions

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

• Treatments

The study intervention marstacimab (PF-06741086) was administered as 300 mg SC (2 \times 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 is not required but, under certain circumstances, is 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.
- **Non-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 coagulation FVIII or FIX over a 6-month period in the absence of a confirmed FVIII or FIX inhibitor, respectively.

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 utilise 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 (eg, ecchymoses, epistaxis).

The investigator will review this criterion with the participant/caregiver at the time study intervention is first dispensed and again at study visits and visits conducted by phone. In the event that this criterion for regimen escalation is met, the participant/caregiver must contact the investigator as soon as possible, and the investigator will confirm that the participant has met the criterion. The investigator will discuss planned regimen escalation with the sponsor's medical monitor and determine new dosing regimen for the participant. The investigator will provide the participant/caregiver with instructions for the new prophylaxis regimen. The participant will now follow the protocol assigned regimen escalation, and arrangements for adequate study intervention supplies will be made.

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

Table 18: Haemostatic medication allowed for use during the study

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;

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 $4 \times$ half-life;
- From FIX replacement therapy for at least 96 hours;
- From extended half-life FIX replacement therapy for at least $4 \times$ 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 stabilised 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 categorised 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 (eg, 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 (eg, 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.

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

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

- **Objectives**

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.

Non-Inhibitor Cohort

For the EU, the statistical hypothesis was the demonstration of *non-inferiority* of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase compared to routine *prophylaxis* during 6 months prior to receiving study intervention, on the difference in the ABR of treated bleeds (non-inferiority margin of 2.5) 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) *without inhibitors* who receive routine *prophylaxis* treatment during the 6 months prior to receiving study intervention. Non-inferiority will be declared if the two-sided 95% confidence interval of the estimated ABR difference (PF-06741086 prophylaxis – prior prophylaxis) lies below 2.5. If non-inferiority is demonstrated on ABR, subsequent testing for superiority will be conducted on this endpoint.

Secondary objectives

Additional efficacy evaluation of PF-06741086

For the Non-Inhibitor Cohort, the primary endpoint with respect to comparisons with prior on-demand therapy for regions outside EU will be a secondary endpoint for the EU.

The following parameters were assessed for comparison between PF- 06741086 prophylaxis observed over the 12-month Active Treatment Phase versus prior prophylaxis therapy or 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)/Pediatric 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])

• **Outcomes/endpoints**

Table 19: 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 $\leq 2\%$, respectively) without inhibitors. Based on the mITT: All participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP). Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing were excluded from mITT.
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)	The annualised bleeding rate (ABR) of treated bleeding events over a 12-month Active Treatment Phase (ATP) compared to a previous 6-month Observational Phase (OP).
Population-level summary	The mean ABR difference (marstacimab prophylaxis – prior prophylactic treatment) based on adult and adolescent participants meeting the entry criteria with prior prophylaxis therapy.
Intercurrent events and strategy to handle them	
Receiving rescue medication in the	Treatment policy

Population	<p>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) without inhibitors.</p> <p>Based on the mITT: All participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).</p> <p>Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing were excluded from mITT.</p>
form of factor replacement or bypass therapy	
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

The hypothesis testing of the primary endpoint is listed below. Type I error rate will be separately controlled within each statistical testing.

For the EU: to demonstrate *non-inferiority* of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase compared to routine *prophylaxis* during 6 months prior to receiving study intervention, on the difference in the ABR of treated bleeds (non-inferiority margin of 2.5) 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) *without inhibitors* who receive routine *prophylaxis* treatment during the 6 months prior to receiving study intervention. Non-inferiority will be declared if the two-sided 95% confidence interval of the estimated ABR difference (PF-06741086 prophylaxis – prior prophylaxis) lies below 2.5. If non-inferiority is demonstrated on ABR, subsequent testing for superiority will be conducted on this endpoint. Note this is a secondary endpoint for regions outside the EU.

The primary objective is addressed via the primary endpoint of ABR of treated bleeds. For the Non-Inhibitor Cohort aiming for the EU, the difference in mean ABRs is estimated between the PF-06741086 prophylaxis for the 12-month Active Treatment Phase during Active Treatment Phase and routine *prophylaxis*.

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.

Intercurrent events: For all cohorts and regions, all data collected while receiving rescue medication in the form of factor replacement or bypass therapy are included. However, all data during the preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours), or collected after dose modification and/or discontinuation of treatment will not be included.

Secondary Objectives Estimands

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

- Sample size**

A sample size of 60 evaluable participants were derived via simulation under a range of scenarios. In the simulation, bleeding counts were generated from a negative binomial distribution with the mean bleeds over 6 months of initially assumed as 2.5. An added scenario of 2.35 was obtained as the weighted average of Haemophilia A and B ABRs based on a meta-analysis of selected historical data among Pfizer haemophilia studies, B1821010 (BeneFIX), B1821002 (BeneFIX), and B1831004 (Xyntha/ReFacto) ($5.1 \cdot 0.8 + 3.1 \cdot 0.2 = 4.7$ ABR); the weights were based on the prevalence of each haemophilia type. The mean bleeds over 12 months for PF-06741086 prophylaxis was initially assumed as 4 with 2 additional scenarios of 2.67 and 3.46, the point estimate and the upper bound of the 1-sided 80% CI from Study B7841002, respectively.

The variance was assumed as 6 times the mean for each scenario; the correlation between the 2 bleeding counts at OP and ATP from the same participant was assumed as 0.2. The simulation further accounted for different follow-up times due to drop-out or lost-to follow-up. To simulate 10% discontinuation during the ATP, a uniform (0, 1) random number U_i was generated for each subject; when $U_i < 0.1$, the duration of treatment was curtailed into $10 \cdot U_i$ years; the number of bleeding X_i in this reduced duration was newly generated from a negative binomial distribution with the expected value of $\mu_i = 10 \cdot U_i \cdot \mu$ and variance of $6 \cdot U_i \cdot \mu$ where μ represents the mean bleeding for PF-06741086 prophylaxis for complete follow up. The Table below demonstrates that the planned sample sizes maintain adequate power (>90%) for all scenarios except for the most pessimistic case.

Table 20: Power simulations with different follow-up

Testing/ Sample Size	Assumed PF-06741086 Mean Bleeding for 12 Months ¹	Assumed Reference Mean Bleeding for 6 Months ²	Simulated Power ³ (%)
Non-inferiority vs prior prophylaxis with N=60	4	2.5	90.1
	3.46		96.9
	2.67		>99
	4	2.35	86.9
	3.46		95.4
	2.67		>99

1. Initial assumption 4; then 3.46 and 2.67 as the upper bound of 80% CI and the point estimate from B7841002.
2. Initial assumption 12.5 and 2.5; then 2.35 as the weighted average (80% and 20%) of haemophilia A and B ABRs from an internal meta-analysis.
3. 5,000 simulations per each scenario where bleed counts were generated from a negative binomial distribution; each variance was assumed to be 6 times the mean with correlation coefficient of 0.2 between 2 bleed counts from the same participants. To simulate 10% discontinuation during the ATP, a uniform (0, 1) random number U_i was generated for each subject; when $U_i < 0.1$, the year of observation was curtailed into $10 \cdot U_i$ years with the number of bleeding X_i newly generated from a negative binomial distribution with the expected value of $\mu_i = 10 \cdot U_i \cdot \mu$ and variance $6 \cdot U_i \cdot \mu$.

- **Randomisation and Blinding (masking)**

This was an open-label study; however, the specific cohort assignment to which a participant was assigned was to be reported using an IVRS/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.

- **Statistical methods**

Analysis Set

For purposes of efficacy analyses, a modified Intent-to-Treat (mITT) Population was defined for this open-label, single arm, 1-way crossover study including all participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors who are treated with routine prophylaxis

in the OP). Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing was excluded from mITT.

The "All Safety" Analysis Set was 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 will be excluded from this population.

Analysis Method

When PF-06741086 prophylaxis treatment is compared with prior routine prophylaxis for various bleeding count endpoints (treated, spontaneous, joint, target joint[s], and all bleeds), a repeated measure negative binomial regression model via GEE approach was used with identity link function. In the model, the number of bleeds will be a response variable, and duration (in years) and the interaction by treatment (PF-06741086 prophylaxis or routine prophylaxis) and duration will be factors with no intercept. The working correlation will be set as Unstructured. Treatment difference in the mean ABRs were obtained using a contrast within the interaction term. Non-inferiority is demonstrated if the upper bound of the 2-sided 95% CI for the mean ABR difference (PF-06741086 prophylaxis – routine prophylaxis) lies below the pre-set non-inferiority margin for each endpoint. If the non-inferiority is established, subsequent testing for superiority may be conducted.

Derivation of non-inferiority Margin for treated bleeds

The derivation followed the methodology outlined in FDA (Food and Drug Administration) Guidance for Non-Inferiority Clinical Trials to Establish Effectiveness.

Historical data were selected among Pfizer haemophilia studies. This enabled selection of individual participant level data that would closely match the inclusion/exclusion criteria of Study B7841005. The following 3 studies satisfied these criteria: B1821010 (BeneFIX), B1821002 (BeneFIX), and B1831004 (Xyntha/ReFacto).

- B1821010 was an open-label 1-way crossover study intended to compare the efficacy and safety between the on-demand treatment and prophylactic therapy using BeneFIX in haemophilia B patients with ages 12-65 years old and the factor IX activities not greater than 2%. This study comprised Period 1 (on-demand treatment at a dosage determined by principal investigator, 6 months) and Period 2 (100 IU/kg once-weekly dose, 12 months).
- B1821002 was an open-label, randomised, 4-period crossover study on males with haemophilia B with ages 6-65 years old and the factor IX activities not greater than 2% to compare on-demand administration and 2 prophylaxis regimens. Study was conducted following 4 periods:
 - Period 1: On-demand administration per dose directed by investigators, 16 weeks.
 - Period 2: 50 IU/kg/ twice weekly or 100 IU/kg/once weekly (randomised), 16 weeks.
 - Period 3: On-demand administration per dose directed by investigators, 8 weeks.
 - Period 4: 50 IU/kg/twice weekly or 100 IU/kg/once weekly (different regimen than that applied during Period 2), 16 weeks.
- B1831004 evaluated safety and efficacy of ReFacto AF in haemophilia A patients switching to ReFacto AF from ReFacto or other factor VIII products in usual care settings. The patients were of ages 12 and greater and had factor XIII activities <1%. All participants were treated under standard care with

ReFacto AF at a dose and frequency prescribed by the treating physician. The duration of treatment depended on the frequency of infusions (to achieve 100 exposure days) with mean (SD) of 336 (223) days.

The analyses included subjects with matching age (12-74 years old) and factor level (<1%) criteria to Study B7841005. The mean ABR difference between prophylaxis and on-demand treatment was estimated using 3 analyses: t-test allowing for non-homogeneous variances, Hodges-Lehman location-shift parameter estimation, and additive negative binomial model. All analyses resulted in similar estimated mean differences and lower bound of 2-sided 95% confidence intervals.

Based on the lower bound of the confidence interval of this estimate, the on-demand ABR was assumed to be higher than M1 in the non-inferiority test setting.

Given the large effect size of prophylaxis treatment, an appropriate value for M2 was considered in order to preserve a sufficiently large proportion of this effect. A value of 2.5 for M2 was selected as both clinically meaningful and yielding a reasonable sample size. M1 and M2 are derived from the notation used in the FDA Guidance document, Non-Inferiority Clinical Trials to Establish Effectiveness.

The process of deriving the non-inferiority margin and the selected magnitude of the margin also satisfy the principles delineated in the EMA/CHMP Guideline on the Choice of the Non-inferiority Margin.

- The estimated effect of factor replacement therapy versus on-demand and its most conservative lower bound of the 95% CI is estimated mean difference and M1, respectively.
- The margin of 2.5 preserves a large portion of the most conservative estimated effect.
- In meta-analyses of factor replacement products to 2017, the weighted mean ABR was 5.1 for factor VIII prophylaxis and 3.1 for factor IX prophylaxis for factor IX prophylaxis, all products have participants with factor level activity $\leq 2\%$, the planned phase 3 <1%; therefore, the non-inferiority margin of 2.5 should be interpreted in the background comparator mean ABR of ~ 4.5 .
- Expected half-width of 95% CI is 2.1 applying the parameter assumptions for the sample size calculation (ABR of 2.5 for 6 months for prior prophylaxis, 4 for 1 year for PF06741086 prophylaxis, variance = 6*mean, correlation = 0.2); therefore, meeting the non-inferiority margin of 2.5 requires that the point estimate for the difference is close to 0; further establishing acceptable efficacy of PF06741086 relative to factor replacement therapy.
- In addition, PF-06741086 has an advantage via once weekly subcutaneous dosing versus up to 2 or 3 times weekly IV dosing of the active comparators. Per guidance, it may be possible to justify a wider non-inferiority margin for efficacy in this case.

Clinically, the planned non-inferiority hypothesis will be met if the difference between PF-06741086 and factor-based prophylaxis regimens does not exceed 2.5. The pooled ABR observed across the 4 cohorts studied in the 3 month phase 2 B7841002 study of PF-06741086-based prophylaxis was 2.6 (N=24).3 Reproducing this result in B7841005 during the active treatment period, and assuming a factor-based prophylaxis ABR of ~ 4.5 during the observation period, would place the upper bound of the 95% CI difference at around and ABR of 5, which is comfortably within the range of ABR achieved with approved factor XIII and IX-based prophylaxis regimens

Further non-inferiority margins for other bleed count and key secondary HRQoL endpoints

Table 21: Key Secondary Endpoints and Decision Rules

Endpoints	Non-Inferiority vs. Prior Prophylaxis for Non-inhibitors
Incidence of spontaneous bleeds	2.5 ABR Difference
Incidence of joint bleeds	2.5 ABR Difference
Incidence of target joint bleeds	1.2 ABR Difference
Incidence of total bleeds	2.9 ABR Difference
Physical health domain in Haem-A-QoL at 6 months	Median Difference: 10 units
Total score in Haem-A-QoL at 6 months*	Median Difference: 7 units
EQ-5D-5L Index score at 6 months*	Median Difference: 0.1 units
EQ-VAS score at 6 months*	Median Difference: 9.5 units

*: These endpoints are key secondary only for the EU, but not for regions outside the EU

Handling Missing Data

The table below describes possible reasons for *incomplete* treatment duration and how each of these are handled in analyses of endpoints related to bleeding counts.

Table 22: Handling Intercurrent Events in Bleed Count Analyses

Reason	Primary analysis of the primary endpoint; analyses of all key secondary endpoints	Sensitivity/supplementary analysis of the primary endpoint
Preventative treatment for medical/dental procedures, sport activity or physical therapy (plus 72 hours)	Exclude	Include
Dose increase of PF-06741086	Exclude	<ol style="list-style-type: none">1. Include the portion after dose increase.2. Impute the prorated duration and the bleeding counts using the data in the primary analysis.3. Tipping point analysis where the observed data are combined with multiples of successively larger

		(>1) portion to determine the tipping point.
Treatment discontinuation	Data collected after treatment discontinuation will be excluded; Analyze observed data during treatment only	<ol style="list-style-type: none"> 1. Impute the prorated duration and the bleeding counts using the data in the primary analysis. 2. Tipping point analysis where the data in the primary analysis are combined with multiples of successively larger (>1) portion to determine the tipping point.

A tertiary endpoint of the number of target joints was derived during the treatment duration excluding the period of preventative treatment for medical/dental procedures, sport activity or physical therapy (plus 72 hours) and the increased dose of PF-06741086.

For the Wilcoxon signed rank test used to analyse physical health domain and the total score of Haem-A-QoL, as well as EQ-5D-5L index score and EQ-VAS scores, a multiple imputation approach with 10 imputations were applied via monotone or fully conditional specification (FCS) regression approach utilizing the 'missing at random' assumption.

The same approach was used for the following endpoints: HJHS total score, Haemo-QoL total score, HAL/pedHAL total score, and PGIC. A single imputation procedure using the month 6 OP value was used for the Wilcoxon signed rank test for the domain and component scores of PRO endpoints.

Sensitivity and Supplementary analyses

Supplemental Analyses

Supplemental analyses used the same methodology and summary as the main analysis but used 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 repeated with the same model, using the following approaches:
 - a. Including the portion of 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 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 assessed the impact of carryover effect from the Observational Phase.
 - a. The main analysis was repeated with the main 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) were descriptively summarised and compared.
2. The following analysis was performed to assess the seasonal effect on bleeding; it used the same methodology and summary as the main analysis but will include only the observations that match the calendar time between OP and ATP.
3. The following summary was provided to assess a potential impact on efficacy assessment due to a 1-way cross-over study design where some participants are excluded from mITT via not successfully completing the OP and/or not meeting the eligibility criteria to enter the ATP.
 - a. disposition of participants who are excluded from mITT
 - b. demography by mITT status – All Safety Set
 - c. subject characteristics by mITT status – All Safety Set
 - d. descriptive summary of the ABR of treated bleeds during OP by mITT status – All Safety Set

No sensitivity or supplemental analyses will be performed for the bleeding-related secondary endpoints.

Planned subgroup analyses

Subgroup analyses were conducted for the primary endpoint for the following variables: Haemophilia A and B, age (12-17 and ≥ 18), race, ethnicity, and geographic region.

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 non-inhibitor cohort for the EU based on participants and each of the other 2 cohorts.

Within each cohort, the familywise Type I error rate for the secondary endpoints was controlled using hierarchical testing method at the 1-sided 0.025 level following the ordering of statistical testing:

Table 23: Ordering of Statistical Testing in Non-Inhibitor Cohort for EU

Endpoints	Non-Inferiority vs. Prior Prophylaxis	Superiority vs. Prior Prophylaxis
Treated bleeds (primary)	1	6
Incidence of spontaneous bleeds	2	12
Incidence of joint bleeds	3	13
Incidence of target joint bleeds	5	15
Incidence of total bleeds	4	14
Physical function domain in Haem-A-QoL	7	11
Total score in Haem-A-QoL at 6 months	8	16
EQ-5D-5L Index score at 6 months	9	17
EQ-VAS score at 6 months	10	18

Interim Analyses

Upon completion of the 12-month ATP for the Non-Inhibitor Cohorts (with prior On-Demand therapy as well as with prior Prophylaxis), analyses of the primary endpoint of interest along with secondary endpoints in the corresponding participant populations were performed to assess respective efficacy and safety for a potential initial registration filing regardless of whether or not follow-up is ongoing in the Inhibitor cohort. These analyses were considered the final analyses for these participant populations. The study will continue until the completion of participants from all cohorts.

Type I error rate of 2-sided 0.05 is allocated separately to each of the 3 populations (Inhibitor Cohort; Non-Inhibitor Cohort with prior On-Demand therapy as well as with prior Prophylaxis). Therefore, analyses upon completion of the Non-Inhibitor Cohorts (with prior On-Demand therapy as well as with prior Prophylaxis) do not impact the Type I error for the Inhibitor Cohort.

Results

- Participant flow**

Table 24: Disposition events summary

Number (%) of Participants	Non-Inhibitor with On-Demand at OP	Non-Inhibitor with Prophylaxis at OP	Overall
	n (%)	n (%)	n (%)
Disposition phase: Screening			
Participants Entered:			179
Discontinued*			50
Reason for discontinuation			
Adverse Event		1 (0.6)	
Death		0	
Lost to Follow-Up		0	
Protocol Deviation		0	
Screen Failure		47 (26.3)	
Study Terminated By Sponsor		0	
Withdrawal By Subject		1 (0.6)	
Withdrawal By Parent/Guardian		1 (0.6)	
Other		0	
Completed		129 (72.1)	
Completed but not Entered OP*		1 (0.6)	
Disposition phase: Observational Phase (OP)			
Participants Entered:	37 (100.0)	91 (100.0)	128 (100.0)
Discontinued	3 (8.1)	7 (7.7)	10 (7.8)
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	2 (5.4)	2 (2.2)	4 (3.1)
Study Terminated By Sponsor	0	0	0
Withdrawal By Subject	0	0	0
Medication Error Without Associated	0	0	0
Adverse Event			
No Longer Meets Eligibility Criteria	0	5 (5.5)	5 (3.9)
Withdrawal By Parent/Guardian	0	0	0
Global Deterioration Of Health Status	0	0	0
Other	1 (2.7)	0	1 (0.8)
Completed	34 (91.9)	84 (92.3)	118 (92.2)
Completed but not Entered ATP	1 (2.7)	1 (1.1)	2 (1.6)
Disposition phase: Active Treatment Phase (ATP)			
Participants Entered:	33 (100.0)	83 (100.0)	116 (100.0)
Discontinued	0	5 (6.0)	5 (4.3)
Reason for discontinuation			
Adverse Event	0	1 (1.2)	1 (0.9)

Number (%) of Participants	Non-Inhibitor with On-Demand at OP	Non-Inhibitor with Prophylaxis at OP	Overall
	n (%)	n (%)	n (%)
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	4 (4.8)	4 (3.4)
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	33 (100.0)	78 (94.0)	111 (95.7)
Plan to Participate in the Extension Study	32 (97.0)	76 (91.6)	108 (93.1)
B7841007			
Disposition phase: Follow-Up			
Participants Entered:	1 (100.0)	8 (100.0)	9 (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	1 (100.0)	8 (100.0)	9 (100.0)

Number (%) of Participants	Non-Inhibitor with On-Demand at OP	Non-Inhibitor with Prophylaxis at OP	Overall
	n (%)	n (%)	n (%)
<p>* Includes both inhibitor and non-inhibitor cohort participants who are in screening, discontinued at screening or completed screening but not entered OP as cohort assignment occurred upon entering the OP.</p> <p>Percentage is calculated based on the number of participants entered at each phase.</p> <p>Participants who discontinued or did not roll over to Study B7841007 were to complete the follow up phase.</p> <p>One participant who screen failed and later rescreened and randomized into the study has also been captured in the total N for screen failed participants, while all other participants who screen failed and later rescreened and randomized into the study were not captured in the total N for screen failed participants.</p> <p>Participant IDs 10221008 and 10221009 represent the same individual. Under Participant ID 10221008, the participant is captured as a screen failure. The participant was rescreened under Participant ID 10221009, completed screening, and was enrolled into the study.</p> <p>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.</p> <p>One participant was shown as completed screening but did not enter OP: At the time of the data cut-off, the inhibitor cohort data was missing because the participant had their enrollment/cohort assignment visit after the data cut-off date.</p> <p>PFIZER CONFIDENTIAL SDTM Creation: 12MAY2023 (11:58) Source Data: add5 Table Generation: 29JUN2023 (08:58)</p> <p>(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File: ./ndal_cdisc/B7841005_LA/add5_s0011</p>			

- Recruitment**

First patient first visit (FPFV): 09 March 2020

Data Cutoff Date (LPLV for Non-inhibitor cohort): 17 April 2023

- 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.

Table 25: Protocol amendments summary of changes 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 $\leq 2\%$) and hemorrhagic phenotype (≥ 4 bleeding episodes in the 6 months prior to study entry).

Allowed additional participants (approximately 20%) in order to provide sufficient enrollment 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

Important protocol deviations

74 (57.8%) participants had important protocol deviations reported, including those related to procedures/tests (31 participants), investigational product (25 participants), concomitant medications (22 participants), informed consent (18 participants), inclusion/exclusion criteria (10 participants), safety reporting (8 participants), laboratory (4 participants), and randomization (1 participant). 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. Participants 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, with the exception of 1 participant who had 1 treated bleed. 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. PROs questionnaires not completed resulted in missing PRO data, however, the impact of the missing data was minimal on the overall analysis of the PRO data. Overall, there was no observed impact to safety or efficacy due to the important protocol deviations.

• 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 enrollment.

Participants in Study B7841005 were primarily White (65, 50.8%) and Asian (61, 47.7%), with 1 Black/African American (0.8%) participant and 1 participant's race not reported. 42.2% and 36.7% of participants were from Asia and Europe, respectively.

Demographic characteristics for participants are summarized in Table 26 below. Table 27 summarises participant haemophilia history by haemophilia type, target joint, and geographical region.

Target joints are defined as major joints (eg, 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). Target joints are a contributing factor to bleeding phenotype, eg, the bleeds from a single target joint would count toward a participant having an ABR of at least 6, the bleeds from 2 target joints would count toward a participant having an ABR of at least 12, and the bleeds from 3 or more target joints would count toward a participant having an ABR of at least 18.

Overall, across participants without inhibitors in Study B7841005:

- 101 (78.9%) participants had haemophilia A and 27 (21.1%) participants had haemophilia B.
- 108 (84.4%) participants were adults (≥ 18 to < 75 years of age) and 20 (15.6%) participants were adolescents (≥ 12 to < 18 years of age).
- 38 (41.8%) participants with prior prophylactic treatment had no target joints at baseline. The remaining 53 out of 91 participants with prior prophylactic treatment had one or more target joints at baseline.
- 1 (2.7%) participant with prior on-demand treatment had no target joints at baseline. The remaining 36 out of 37 participants with prior on-demand treatment had one or more target joints at baseline.

All 128 participants were male with a median age of 30.0 years and individual values ranged from 13.0 to 66.0 years. The majority of participants (78, 60.9%) were in the 18-44 age range.

The median participant weight was 70.7 kg (range: 35.0 to 120.0 kg) and the median participant BMI was 24.1 kg/m² (range: 15.2 to 38.8 kg/m²). The median participant height was 170.1 cm (range: 141.0 to 190.0 cm).

Most participants (100, 78.1%) had normal renal function (eGFR ≥ 90 mL/min/1.73 m²), while 24 (18.8%) participants had mild renal impairment (eGFR ≥ 60 to < 90 mL/min/1.73 m²) and 1 (0.8%) participant had moderate renal impairment (eGFR 30 to < 60 mL/min/1.73 m²).

Table 26: Baseline and demographic characteristics – all safety set

	Non-Inhibitor with On-Demand at OP (N=37)	Non-Inhibitor with Prophylaxis at OP (N=91)	Overall (N=128)
Age (Years), n (%)			
< 18	2 (5.4)	18 (19.8)	20 (15.6)
18 - 44	31 (83.8)	47 (51.6)	78 (60.9)
45 - 64	4 (10.8)	25 (27.5)	29 (22.7)
65 - 74	0	1 (1.1)	1 (0.8)
≥ 75	0	0	0
n	37	91	128
Mean (SD)	31.4 (10.54)	33.0 (14.76)	32.5 (13.65)
Median	29.0	31.0	30.0
(Q1, Q3)	(24.0, 37.0)	(18.0, 45.0)	(21.0, 44.0)
(Min, Max)	(15.0, 58.0)	(13.0, 66.0)	(13.0, 66.0)
Sex, n (%)			

Male	37 (100.0)	91 (100.0)	128 (100.0)
Race, n (%)			
Black or African American	0	1 (1.1)	1 (0.8)
American Indian or Alaska Native	0	0	0
Asian	24 (64.9)	37 (40.7)	61 (47.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	13 (35.1)	52 (57.1)	65 (50.8)
Not Reported	0	1 (1.1)	1 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	4 (10.8)	9 (9.9)	13 (10.2)
Not Hispanic or Latino	33 (89.2)	82 (90.1)	115 (89.8)
Baseline eGFR* (mL/min/1.73m ²), n (%)			
≥ 90	32 (86.5)	68 (74.7)	100 (78.1)
≥ 60 to < 90	5 (13.5)	19 (20.9)	24 (18.8)
≥ 30 to < 60	0	1 (1.1)	1 (0.8)
< 30	0	0	0
Missing	0	3 (3.3)	3 (2.3)
Weight (kg)			
n	37	91	128
Mean (SD)	70.2 (19.35)	70.1 (15.13)	70.1 (16.38)
Median	71.0	70.4	70.7
(Q1, Q3)	(54.0, 78.7)	(61.8, 80.0)	(58.3, 79.7)
(Min, Max)	(43.2, 114.0)	(35.0, 120.0)	(35.0, 120.0)
Height (cm)			
n	37	91	128
Mean (SD)	171.5 (8.78)	170.7 (8.32)	171.0 (8.43)
Median	170.0	170.7	170.1
(Q1, Q3)	(167.0, 176.0)	(166.5, 178.0)	(166.8, 177.0)
(Min, Max)	(157.2, 190.0)	(141.0, 185.0)	(141.0, 190.0)
Body Mass Index (kg/m ²)			
n	37	91	128
Mean (SD)	23.7 (5.61)	23.9 (4.22)	23.8 (4.64)
Median	24.4	24.0	24.1
(Q1, Q3)	(18.7, 27.3)	(21.2, 26.6)	(20.8, 26.8)
(Min, Max)	(15.3, 38.8)	(15.2, 36.0)	(15.2, 38.8)

Age at Screening (years) = (year of given informed consent - year of birth).

The denominator to calculate percentages is N, the number of participants in the all safety set within each reporting group. All safety set is defined as those participants in the non-inhibitor cohort with prophylaxis at OP who received at least one prophylactic or on-demand treatment during the OP and those participants in the non-inhibitor cohort with on-demand treatment at OP who completed any of the Visit 2 procedures (OP baseline).

n is the number of participants with non-missing observation.

Body Mass Index (kg/m²) = weight (kg) / [height (cm) x 0.01]².

* Estimated Glomerular Filtration Rate (eGFR) using Modification of Diet in Renal Disease (MDRD) method for adult participants; eGFR using Ped Schwartz method for adolescent participants.

A total of 21 adolescents were eligible for the all safety set. The data regarding 1 adolescent participant from the non-inhibitor cohort with prophylactic treatment at OP was excluded from the All Safety Analysis Set due to GCP non-compliance leading to termination of study site.

PFIZER CONFIDENTIAL SDTM Creation: 12MAY2023 (11:58) Source Data: ads1 Table Generation: 20JUN2023 (11:42)

(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File:
/nda1 cdisc/B7841005 IA/ads1 s001

Table 27: Participants characteristics – all safety set

	Non-Inhibitor with On-Demand at OP (N=37)	Non-Inhibitor with Prophylaxis at OP (N=91)	Overall (N=128)
Hemophilia Type, n (%)			
Hemophilia A	29 (78.4)	72 (79.1)	101 (78.9)
Hemophilia B	8 (21.6)	19 (20.9)	27 (21.1)
Age Groups, n (%)			
Adolescents (Ages 12 to < 18)	2 (5.4)	18 (19.8)	20 (15.6)
Adults (Ages 18 to < 75)	35 (94.6)	73 (80.2)	108 (84.4)
Age and Hemophilia Type, n (%)			
Adolescents Hem A	2 (5.4)	13 (14.3)	15 (11.7)
Adolescents Hem B	0	5 (5.5)	5 (3.9)
Adults Hem A	27 (73.0)	59 (64.8)	86 (67.2)
Adults Hem B	8 (21.6)	14 (15.4)	22 (17.2)
Factor VIII Inhibitor at Baseline, n (%)			
Participants with Hemophilia A	29 (100.0)	72 (100.0)	101 (100.0)
Positive	0	0	0
Negative	29 (100.0)	72 (100.0)	101 (100.0)
Factor IX Inhibitor at Baseline, n (%)			
Participants with Hemophilia B	8 (100.0)	19 (100.0)	27 (100.0)
Positive	0	0	0
Negative	8 (100.0)	19 (100.0)	27 (100.0)
ISTH Disease Severity, n (%)			
Mild	0	0	0
Moderate	1 (2.7)	0	1 (0.8)
Severe	36 (97.3)	91 (100.0)	127 (99.2)
Number of Target Joints at Baseline, n (%)			
0	1 (2.7)	38 (41.8)	39 (30.5)
1	8 (21.6)	21 (23.1)	29 (22.7)
2	16 (43.2)	15 (16.5)	31 (24.2)
≥ 3	12 (32.4)	17 (18.7)	29 (22.7)
Geographical Region, n (%)			
Asia	23 (62.2)	31 (34.1)	54 (42.2)
Europe	8 (21.6)	39 (42.9)	47 (36.7)
Middle East	2 (5.4)	10 (11.0)	12 (9.4)
North America	4 (10.8)	11 (12.1)	15 (11.7)

All safety set is defined as those participants in the non-inhibitor cohort with prophylaxis at OP who received at least one prophylactic or on-demand treatment during the OP and those participants in the non-inhibitor cohort with on-demand treatment at OP who completed any of the Visit 2 procedures (OP baseline).

A total of 21 adolescents were eligible for the all safety set. The data regarding 1 adolescent participant from the non-inhibitor cohort with prophylactic treatment at OP was excluded from the all safety set due to GCP non-compliance leading to termination of study site.

PFIZER CONFIDENTIAL SDTM Creation: 27JUL2023 (16:30) Source Data: adsl Table Generation: 27JUL2023 (16:37)
(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File:
/ndal1_cdisc/B7841005_IA/adsl_s001_si

Medical History and Concurrent Illnesses

The most common conditions in study participants ($\geq 5\%$) were hepatitis (27 [21.1%] with hepatitis C, 8 [6.3%] with hepatitis B, and 4 [3.1%] with chronic hepatitis C), haemophilic arthropathy (20, 15.6%), hypertension (16, 12.5%), circumcision (13, 10.2%), synoviorthesis (10, 7.8%), and arthropathy (7, 5.5%: 6 of whom also reported haemophilic arthropathy and 1 participant had unspecific arthropathy). One participant in the prior prophylaxis group with a medical history of cerebral venous sinus thrombosis was discontinued during the OP due to this inclusion/exclusion protocol deviation.

• Numbers analysed

Overall, 179 participants were screened, of whom 50 participants discontinued (47 participants failed at screening, 1 participant withdrew, 1 participant due to AE, and 1 participant was withdrawn by parent/guardian). Among the 129 participants who completed screening, 128 entered the OP (1 participant completed screening but did not enter the OP: At the time of the data cut-off, the inhibitor cohort data was missing because the participant had their enrollment/cohort assignment visit after the data cut-off date).

As of 17 April 2023, the LPLV for the non-inhibitor cohort:

- 37 participants with prior on-demand treatment using factor replacement entered the study, of whom 34 (91.9%) completed the 6-month OP and 3 (8.1%) discontinued during the OP (2 participants due to protocol deviations and 1 participant due to other reason of moving to a different country). Of the 34 participants who completed the OP, 33 participants entered the ATP and all 33 (100%) participants completed the 12-month ATP. No participants discontinued during the ATP.
- 91 participants with prior prophylactic treatment using factor replacement entered the study, of whom 84 (92.3%) completed the 6-month OP and 7 (7.7%) discontinued during the OP (5 participants no longer met eligibility criteria and 2 participants due to protocol deviations). Of the 84 participants who completed the OP, 83 participants entered the ATP, of whom 78 (94.0%) completed the 12-month ATP and 5 (6.0%) discontinued (4 participants withdrew and 1 participant due to AE).
- 108 of 111 participants who completed the 12-month marstacimab ATP planned to participate in the long-term extension Study B7841007.
- 1 participant with prior on-demand treatment and 8 participants with prior prophylactic treatment entered the follow-up phase of Study B7841005. Note: participants who planned to participate in the long-term extension Study B7841007 were not required to enter the follow-up phase.
- Two participants (1 in the prior on-demand cohort and 1 in the prior prophylaxis cohort) completed the OP, but discontinued before entering the ATP and marstacimab dosing due to not meeting eligibility criteria to enter the ATP.

- Outcomes and estimation

Primary Efficacy Endpoint

ABR of Treated Bleeds (Routine Prophylaxis at OP)

Table 28: Primary analysis of the ABR for treated bleeds for non-inhibitor cohort with routine prophylaxis at OP -MITT set

ABR ¹	Routine Prophylaxis During OP (N=83)	Marstacimab Prophylaxis During ATP (N=83)
Descriptive Summary		
Mean	7.88	5.17
SD	12.914	8.041
Median	2.16	2.02
Q1, Q3	0.00, 9.87	0.00, 6.09
Min, Max	0.00, 59.51	0.00, 35.51
Categorical Summary		
Completed the Phase	83 (100.0)	78 (94.0)
0 bleed	33 (39.8)	29 (34.9)
1 bleed	9 (10.8)	7 (8.4)
2 bleeds	11 (13.3)	9 (10.8)
≥ 3 bleeds	30 (36.1)	33 (39.8)
Discontinued the Phase	0 (0.0)	5 (6.0)
Model-based Summary²		
Mean Estimate	7.85	5.08
95% CI	(5.09, 10.61)	(3.40, 6.77)

Treatment Comparison: Marstacimab vs. Routine Prophylaxis³

Difference Estimate	-2.77
95% CI ⁴	(-5.37, -0.16)
p-value ⁴	0.0376
% reduction from OP (95% CI) ⁵	35.2 (5.6, 55.6)

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 identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

3. Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

4. P-value for the null hypothesis of difference=0.

5. Supplemental statistics derived as (1-ratio)*100; The ratio and 95% CI were obtained from 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 routine prophylaxis) as a factor, and log time on treatment as an offset variable to account for different duration on treatment.

ABR of Treated Bleeds (On-Demand at OP)

Table 29: primary analysis of the ABR for treated bleeds for non0inhibitor cohort with on demand of OP- MITT set

ABR ¹	On-Demand During OP (N=33)	Marstacimab Prophylaxis During ATP (N=33)
Descriptive Summary		
Mean	38.05	3.19
SD	22.917	3.919
Median	35.73	2.02
Q1, Q3	18.47, 55.21	0.00, 4.25
Min, Max	0.00, 83.43	0.00, 16.48
Categorical Summary		
Completed the Phase	33 (100.0)	33 (100.0)
0 bleed	1 (3.0)	10 (30.3)
1 bleed	0 (0.0)	4 (12.1)
2 bleeds	0 (0.0)	7 (21.2)
≥ 3 bleeds	32 (97.0)	12 (36.4)
Discontinued the Phase	0 (0.0)	0 (0.0)
Model-based Summary²		
Mean Estimate	38.00	3.18
95% CI	(31.03, 46.54)	(2.09, 4.85)
Treatment Comparison based on the Marstacimab/On-demand ratio²		
Ratio Estimate		0.084
95% CI ³		(0.059, 0.119)
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 log 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 below 0.5.

4. P-value for the null hypothesis that the ratio=0.5.

PFIZER CONFIDENTIAL SDTM Creation: 25MAY2023 (07:38) Source Data: adabr Table Generation: 25MAY2023 (07:38)

(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File:

/ndab1_cdisc/B7841005_1A/adhe_s1001

Table 14.2.1.1.1 Marstacimab is for Pfizer internal use.

Secondary Efficacy Endpoints

Incidence of Joint Bleeds (Routine Prophylaxis at OP)

Table 30: Analysis of incidence of joint bleeds for non-inhibitor cohort with routine prophylaxis at OP-MITT set

ABR ¹	Routine Prophylaxis During OP (N=83)	Marstacimab Prophylaxis During ATP (N=83)
Descriptive Summary		
Mean	5.68	4.20
SD	10.901	7.304
Median	1.89	1.02
Q1, Q3	0.00, 5.92	0.00, 5.04
Min, Max	0.00, 55.89	0.00, 33.48
Categorical Summary		
Completed the Phase	83 (100.0)	78 (94.0)
0 bleed	40 (48.2)	33 (39.8)
1 bleed	12 (14.5)	9 (10.8)
2 bleeds	8 (9.6)	9 (10.8)
≥ 3 bleeds	23 (27.7)	27 (32.5)
Discontinued the Phase	0 (0.0)	5 (6.0)
Model-based Summary²		
Mean Estimate	5.66	4.13
95% CI	(3.33, 7.98)	(2.59, 5.67)
Treatment Comparison: Marstacimab vs. Routine Prophylaxis³		
Difference Estimate		-1.53
95% CI ³		(-3.70, 0.64)
p-value ⁴		0.1680

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 identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

3. Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

4. P-value for the null hypothesis of difference=0.

Incidence of Spontaneous Bleeds (Routine Prophylaxis at OP)

Table 31: analysis of incidence of spontaneous bleeds for non-inhibitor cohort with routine prophylaxis at OP- MIIT set

ABR ¹	Routine Prophylaxis During OP (N=83)	Marstacimab Prophylaxis During ATP (N=83)
Descriptive Summary		
Mean	5.89	3.85
SD	10.868	7.262
Median	1.94	1.01
Q1, Q3	0.00, 6.05	0.00, 4.73
Min, Max	0.00, 53.89	0.00, 35.51
Categorical Summary		
Completed the Phase	83 (100.0)	78 (94.0)
0 bleed	40 (48.2)	35 (42.2)
1 bleed	12 (14.5)	12 (14.5)
2 bleeds	7 (8.4)	6 (7.2)
≥ 3 bleeds	24 (28.9)	25 (30.1)
Discontinued the Phase	0 (0.0)	5 (6.0)
Model-based Summary²		
Mean Estimate	5.86	3.78
95% CI	(3.54, 8.19)	(2.25, 5.31)
Treatment Comparison: Marstacimab vs. Routine Prophylaxis³		
Difference Estimate		-2.09
95% CI ³		(-4.23, 0.06)
p-value ⁴		0.0566

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 identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

3. Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.5. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

4. P-value for the null hypothesis of difference=0.

Incidence of Target Joint Bleeds (Treated) (Routine Prophylaxis at OP)

Table 32: Analysis of incidence of target joint bleeds for non-inhibitor cohort with routine prophylaxis at OP- MIIT set

ABR ¹	Routine Prophylaxis During OP (N=83)	Marstacimab Prophylaxis During ATP (N=83)
Descriptive Summary		
Mean	3.38	2.55
SD	8.317	5.954
Median	0.00	0.00
Q1, Q3	0.00, 1.97	0.00, 1.38
Min, Max	0.00, 38.86	0.00, 27.24
Categorical Summary		
Completed the Phase	83 (100.0)	78 (94.0)
0 bleed	62 (74.7)	54 (65.1)
1 bleed	4 (4.8)	6 (7.2)
2 bleeds	3 (3.6)	4 (4.8)
≥ 3 bleeds	14 (16.9)	14 (16.9)
Discontinued the Phase	0 (0.0)	5 (6.0)
Model-based Summary²		
Mean Estimate	3.36	2.51
95% CI	(1.59, 5.14)	(1.25, 3.76)
Treatment Comparison: Marstacimab vs. Routine Prophylaxis³		
Difference Estimate		-0.86
95% CI ³		(-2.41, 0.70)
p-value ⁴		0.2811
<p>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.</p> <p>2. Based on a repeated measure negative binomial regression model via generalized estimating equation approach with identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.</p> <p>3. Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 1.2. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.</p> <p>4. P-value for the null hypothesis of difference=0.</p>		
<p>PFIZER CONFIDENTIAL SDTM Creation: 12MAY2023 (11:58) Source Data: adabt Table Generation: 07JUN2023 (15:12)</p> <p>(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File: ./nda1_cdisc/B7841005_IA/adhe_s2008</p> <p>Table 14.2.2.2.3 Marstacimab is for Pfizer internal use.</p>		

Incidence of Total Bleeds (Treated and Untreated) (Routine Prophylaxis at OP)

Table 33: Analysis of incidence of total bleeds (treated and untreated) for non-inhibitor cohort with routine prophylaxis at OP -MITT set

ABR ¹	Routine Prophylaxis During OP (N=83)	Marstacimab Prophylaxis During ATP (N=83)
Descriptive Summary		
Mean	8.87	6.06
SD	13.462	8.733
Median	3.91	2.89
Q1, Q3	0.00, 11.66	0.00, 7.04
Min, Max	0.00, 59.51	0.00, 37.54
Categorical Summary		
Completed the Phase	83 (100.0)	78 (94.0)
0 bleed	28 (33.7)	22 (26.5)
1 bleed	9 (10.8)	10 (12.0)
2 bleeds	13 (15.7)	7 (8.4)
≥ 3 bleeds	33 (39.8)	39 (47.0)
Discontinued the Phase	0 (0.0)	5 (6.0)
Model-based Summary²		
Mean Estimate	8.84	5.97
95% CI	(5.97, 11.72)	(4.13, 7.81)
Treatment Comparison: Marstacimab vs. Routine Prophylaxis³		
Difference Estimate		-2.87
95% CI ⁴		(-5.61, -0.12)
p-value ⁴		0.0406

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 identity link function, the working correlation was set as unstructured. The model used the number of bleeds as a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or routine prophylaxis) and duration as factors without intercept.

3. Non-inferiority of marstacimab prophylaxis is declared when the upper bound the 95% CI lies below 2.9. If non-inferiority is established, then a testing for superiority is to be conducted. Superiority is declared when the upper bound of the 95% CI lies below 0.

4. P-value for the null hypothesis of difference=0.

Haemophilia Joint Health Score (HJHS) (Routine Prophylaxis at OP)

Table 34: Non-parametric analysis of change from baseline in haemophilia joint health score (HJHS)* for non-inhibitor cohort with routine prophylaxis at OP – MITT set

HJHS Total Score		Prophylaxis During OP (N=83) ²	Marstacimab Prophylaxis During ATP (N=83)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	1.3	-0.6
	95% CI	(-0.7, 3.3)	(-2.2, 1.0)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference		-2.0
	95% CI		(-4.3, 0.3)
	p-value		0.0835
	Effect Size ³		0.11
Change from Baseline at 12 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	1.3	-0.9
	95% CI	(-0.7, 3.3)	(-2.5, 0.7)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference		-2.2
	95% CI		(-4.8, 0.3)
	p-value		0.0836

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: 12MAY2023 (11:58) Source Data: fahj Table Generation: 26JUN2023 (22:49)

(Data cutoff date : 17APR2023 Database snapshot date : 05MAY2023) Output File:

/ndal1 cdisc/B7841005 IA/adhj s003

Table 14.2.2.2.7 Marstacimab is for Pfizer internal use.

Health-Related Quality-of-Life Outcomes (Routine Prophylaxis 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 ATP is at 6 months, and the 12-month comparison utilises 6-month results from the OP.

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

Table 35: Non-parametric analysis of change from baseline in total score and physical health domain in Haem- A- QoL * for non-inhibitor cohort with prophylaxis at OP -MIIT set

Total Score		Prophylaxis During OP (N=63) ²	Marstacimab Prophylaxis During ATP (N=63)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary ¹		
Median Estimate		-1.2	-3.7
95% CI		(-3.5, 1.1)	(-6.8, -0.6)
Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis			
Estimated Median Difference			-2.8
95% CI			(-6.6, 1.0)
p-value			0.1493
Effect Size ³			0.17
Change from Baseline at 12 Months of Treatment	Non-parametric Summary ¹		
Median Estimate		-1.2	-4.9
95% CI		(-3.5, 1.1)	(-8.1, -1.7)
Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis			
Estimated Median Difference			-3.7
95% CI			(-8.3, 0.9)
p-value			0.1113

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.

* Assessed for participants 17 to < 75 years of age.

Transformed Scale Score is reported; it ranges from 0 to 100 with higher score indicating worse quality of life.

Non-inferiority criterion for the total score was upper bound of 95% CI < 7 ; it was upper bound of 95% CI < 10 for the physical health score.

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.

Table 36: Non-parametric analysis of change from baseline in total score and physical health domain in Haem-A-QoL* for non-inhibitor cohort with prophylaxis at OP-MITT set

Physical Health		Prophylaxis During OP (N=63) ²	Marstacimab Prophylaxis During ATP (N=63)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	-3.0	-6.1
	95% CI	(-8.2, 2.2)	(-12.6, 0.4)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	-2.2	
	95% CI		(-9.1, 4.6)
	p-value		0.5223
	Effect Size ³		0.08
Change from Baseline at 12 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	-3.0	-8.3
	95% CI	(-8.2, 2.2)	(-15.4, -1.3)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	-5.0	
	95% CI		(-12.4, 2.4)
	p-value		0.1848

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.

* Assessed for participants 17 to < 75 years of age.

Transformed Scale Score is reported; it ranges from 0 to 100 with higher score indicating worse quality of life.

Non-inferiority criterion for the total score was upper bound of 95% CI < 7; it was upper bound of 95% CI < 10 for the physical health score.

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.

EQ-5D-5L (Routine Prophylaxis at OP)

Table 37: Non-parametric analysis of change from baseline in EQ-5D for non-inhibitor cohort with routine prophylaxis at OP- MITT set

EQ-5D-5L index ²		Prophylaxis During OP (N=83) ⁴	Marstacimab Prophylaxis During ATP (N=83)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	0.0300	0.0752
	95% CI	(-0.0140, 0.0740)	(0.0178, 0.1325)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	0.0223	
	95% CI		(-0.0432, 0.0877)
	p-value		.5050
	Effect Size ⁵		0.12
Change from Baseline at 12 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	0.0300	0.0640
	95% CI	(-0.0140, 0.0740)	(0.0088, 0.1192)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	0.0226	
	95% CI		(-0.0421, 0.0874)
	p-value		.4932

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. 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.
 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.
- Non-inferiority criterion for the EQ-5D-5L index was lower bound of 95% CI > -0.1; it was lower bound of 95% CI > -9.5 for the EQ-VAS.

Table 38: Non-parametric analysis of change from baseline in EQ-5D for non-inhibitor cohort with routine prophylaxis at OP- MITT set

EQ-VAS ³		Prophylaxis During OP (N=83) ⁴	Marstacimab Prophylaxis During ATP (N=83)
Change from Baseline at 6 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	3.0	4.5
	95% CI	(-0.6, 6.6)	(1.4, 7.7)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	0.6	
	95% CI		(-4.0, 5.1)
	p-value		.8006
	Effect Size ⁵		0.03
Change from Baseline at 12 Months of Treatment	Non-parametric Summary ¹		
	Median Estimate	3.0	3.0
	95% CI	(-0.6, 6.6)	(-0.2, 6.2)
	Treatment Comparison ¹ : Marstacimab - Routine Prophylaxis		
	Estimated Median Difference	-1.5	
	95% CI		(-6.9, 3.8)
	p-value		.5776

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. 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.
 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.
- Non-inferiority criterion for the EQ-5D-5L index was lower bound of 95% CI > -0.1; it was lower bound of 95% CI > -9.5 for the EQ-VAS.

- **Ancillary analyses**

Subgroup Analysis: ABR of Treated Bleeds (Routine Prophylaxis at OP)

ABRs of treated bleeds, when compared with prior prophylaxis treatment for participants without inhibitors, are summarised by haemophilia types and age groups in the Figure below.

All point estimates of the differences across subgroups were consistently under 2.5, the non-inferiority margin for the primary analysis. The upper bound of the CI for some subgroups exceeded 2.5 owing to the small sample size within subgroups.

The descriptive mean ABR of treated bleeds for participants with haemophilia A was 5.30 for marstacimab prophylaxis during the ATP compared to the mean ABR of 9.16 for prior routine prophylaxis during the OP. Out of 65 participants with haemophilia A, 5 participants increased their dose to 300 mg SC QW, and of these, 4 had reductions in their ABRs and 1 maintained their ABR after the dose increase. The mean ABR for all 65 participants with haemophilia A during the entire ATP including the data following the dose increase was 4.95. 60 out of 65 participants completed the ATP.

The upper bound of the CI for the ABR difference among adolescent participants (N=17) and participants with haemophilia B (N=18) exceeded 2.5. It should be noted that the sample size within these subgroups is small and the study was not powered to draw statistical conclusions on subgroups.

The descriptive mean ABR of treated bleeds for adolescent participants was 2.98 for marstacimab prophylaxis during the ATP compared to the mean ABR of 3.30 for routine prophylaxis during the OP. All adolescent participants in the mITT population (N=17) completed the ATP.

The subgroup of haemophilia B adolescents (N=4) displayed significant variability during the ATP, with 2 participants experiencing zero treated bleeds and 2 participants with ABRs of 19.48 (majority traumatic bleeds) and 11.01 (majority traumatic bleeds) during the ATP. All 4 of these participants completed the ATP.

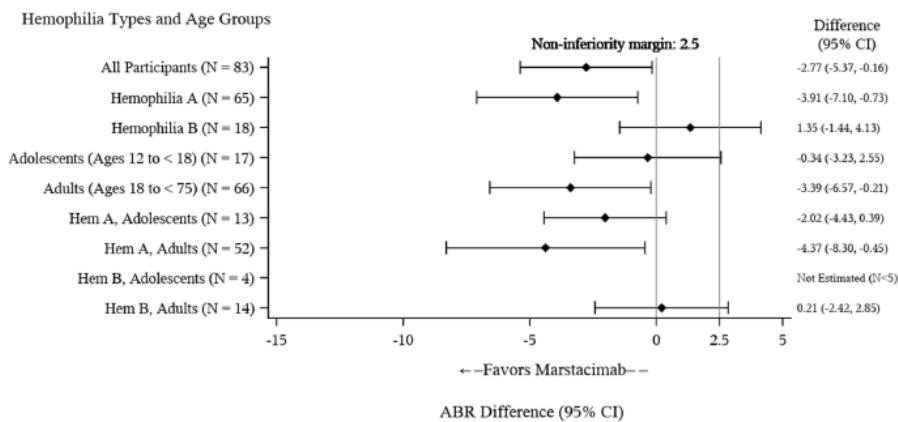
The descriptive mean ABR of treated bleeds for participants with haemophilia B was 4.71 for marstacimab prophylaxis during the ATP compared to the mean ABR of 3.26 for routine prophylaxis during the OP. Out of 18 participants with haemophilia B, 6 participants increased their dose and all had reductions in their ABRs after the dose increase. The mean ABR for all 18 participants with haemophilia B during the entire ATP including the data following the dose increase was 3.88 indicating similar bleed control compared to routine prophylaxis. All 18 participants completed the ATP.

Compliance to the prescribed treatment regimen during the OP and ATP was >90% for all prior prophylaxis cohort haemophilia B participants.

Baseline characteristics of bleeding phenotype severity were similar across haemophilia and age subgroups with the exception of the number of target joints at baseline between the prior prophylaxis cohort adolescent and adult subgroups.

Incidence of ≥ 1 target joints at baseline for adolescents was 27.8% compared to 65.8% for adults in the prior prophylaxis cohort.

Figure 23: Comparison of ABRs for treated bleeds for Haemophilia types and age groups for non-inhibitor cohort with routine prophylaxis at OP- MITT set



The descriptive mean ABRs of treated bleeds during the ATP were generally similar among racial subgroups (Black or African American [4.73, N=1], Asian [6.54, N=36], White [4.15, N=45], Not Reported [2.32, N=1]). The descriptive mean ABRs of treated bleeds during the ATP are numerically lower in North America (2.57, N=11) and Middle East (2.98, N=10) geographic regions, followed by Europe (4.52, N=32), and numerically higher in Asia (7.55, N=30).

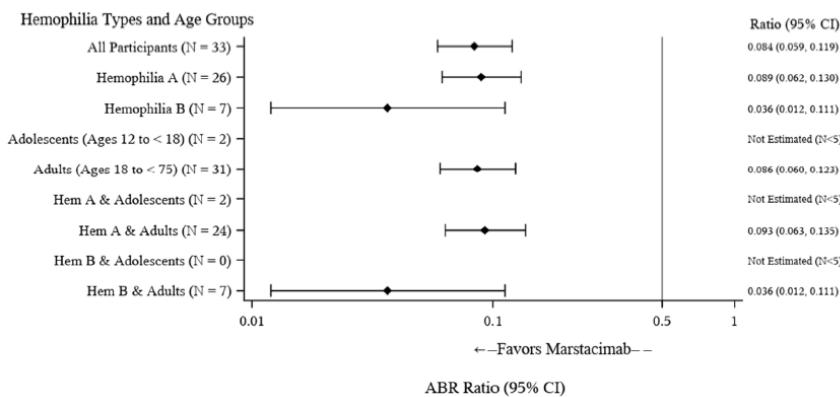
Subgroup Analysis: ABR of Treated Bleeds (On-Demand at OP)

A comparison of the ABRs of treated bleeds for participants without inhibitors and with prior on-demand treatment is summarised by haemophilia types and age groups in the Figure below.

The descriptive mean ABR of treated bleeds for participants with haemophilia A was 3.61 for marstacimab prophylaxis during the ATP compared to the mean ABR of 40.57 for on-demand treatment during the OP. When the marstacimab dose regimen is considered including the data after the dose increase, the mean ABR for participants with haemophilia A during the ATP was 3.64.

The descriptive mean ABR of treated bleeds for participants with haemophilia B was 1.65 for marstacimab prophylaxis during the ATP compared to the mean ABR of 28.67 for on- demand treatment during the OP. When the marstacimab dose regimen is considered including the data after the dose increase, the mean ABR for participants with haemophilia B during the ATP was 1.16.

Figure 24: Comparison of ABRs for treated bleeds for Haemophilia types and age groups for non-inhibitor cohort with on- demand at OP -MITT set



Supplementary/Sensitivity Analysis: ABR of Treated Bleeds (Routine Prophylaxis at OP)

Supplementary/sensitivity analyses of the ABR of treated bleeds for participants without inhibitors and with prior routine prophylaxis are summarised below.

Table 39: Supplementary analysis/sensitivity analyses of the ABRs for treated bleeds for non-inhibitor cohort with routine prophylaxis at OP- MITT set

Supplementary Analysis Type	Estimated ABR ¹ Difference: Marstacimab – Routine Prophylaxis	95% CI
Analysis to assess the impact of preventative infusion		
Including bleeding during preventitave infusion	-2.82	(-5.43, -0.20)
Analyses to assess the impact of marstacimab dose increase		
Number of participants with dose increase: 11		
Including data after a dose increase	-3.20	(-5.82, -0.58)
Imputing the portion after a dose increase using the data before the dose increase	-2.74	(-5.35, -0.13)
Tipping point analysis ²	Tipping Multiplier: 4.4	
	-0.68	(-3.92, 2.55)
Analyses to assess the impact of treatment discontinuation		
Number of participants with ATP discontinuation or dosing gap (≥ 35 days) during which time no bleed was reported: 6		
Including the portion after treatment discontinuation using the data during treatment and during dosing gap using the data before and after the dosing gap	-3.12	(-5.73, -0.51)
Tipping point analysis ²	Tipping Multiplier: 4.6	
	-1.23	(-5.00, 2.53)
Analysis to assess the carryover effect from the observational phase		
Excluding the first month data after initiation of marstacimab	-2.56	(-5.26, 0.13)
Analysis to assess the seasonal effect on bleeding		
Include only the portion of ATP that match the calendar time of OP	-4.40	(-7.10, -1.70)

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 the mean ABR calculated based on bleeds before or outside of the intercurrent event and assuming the mean ABR after or during the intercurrent event as multiples of successively larger (> 1) factors of the former.

Note: All analyses used the same model used in the primary efficacy analysis.

Table 40: Descriptive summary of the ABR for treated bleeds for the first and second half of ATP for completed participants for non-inhibitor with routine prophylaxis at OP-MITT set

ABR ¹ Descriptive Summary	First Half of ATP ² (N=83)	Second Half of ATP ² (N=83)
N Completers ³	67	67
Mean	3.54	2.82
SD	6.956	5.986
Median	0.00	0.00
Q1, Q3	0.00, 3.99	0.00, 2.08
Min, Max	0.00, 39.92	0.00, 30.95

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.

Table 41: Descriptive summary of the ABR for treated bleeds and treatment duration before and after the dose increase for participants with dose for non-inhibitor increase

Descriptive Summary	Before Dose Increase (N=83)	On or After the Dose Increase (N=83)
Treatment Duration (days)		
N with Dose Increase	11	11
Mean	247.0	117.6
SD	56.71	57.36
Median	251.0	108.0
Q1, Q3	190.0, 300.0	65.0, 178.0
Min, Max	175.0, 315.0	52.0, 185.0
ABR ¹		
N with Dose Increase	11	11
Mean	14.03	3.42
SD	8.916	3.992
Median	11.24	2.02
Q1, Q3	7.69, 19.48	0.00, 4.68
Min, Max	2.32, 30.95	0.00, 11.24

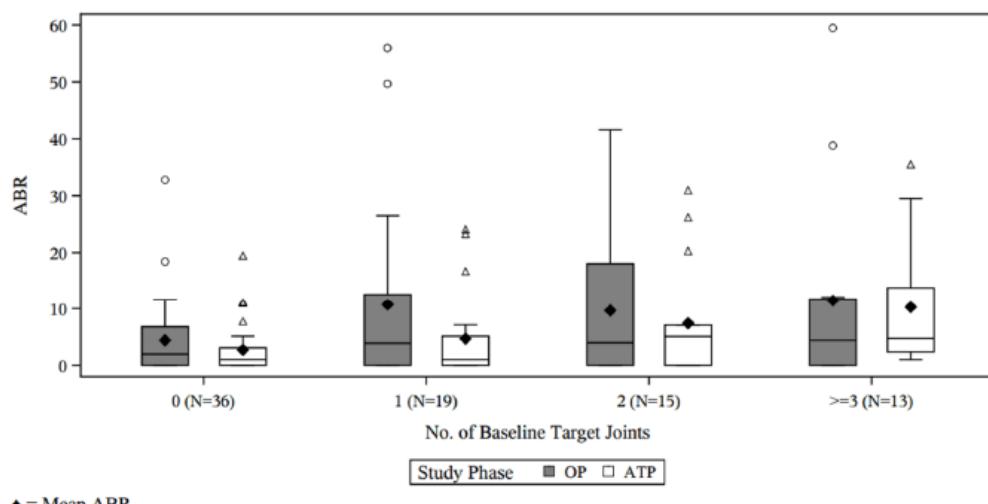
1. ABR= annualized bleeding rate calculated as the number of bleeds requiring treatment/(days on treatment period / 365.25). If a participant did not complete a treatment period, the days on treatment ended at the last dosing date + 6 days.

Post-hoc Sensitivity Analyses: ABR of Treated Bleeds (Routine Prophylaxis at OP)

Post-hoc sensitivity analyses were performed to provide additional context for the results of the ABR of treated bleeds. The figure below compares the ABRs of treated bleeds during the OP versus the ATP by the number of target joints at the OP baseline. The plot displays the following:

- 47 out of 83 participants had at least one target joint at the OP baseline.
- Participants with target joints at the OP baseline tend to have higher ABRs during both the OP and the ATP compared to those without target joints at the OP baseline.
- Mean ABR values were numerically lower in the ATP compared to the OP by number of target joints at OP baseline.

Figure 25: ABRs at OP and ATP by number of target joints at OP baseline for non-inhibitor cohort with prophylaxis at OP-MITT set



♦ = Mean ABR

Figure 26: ATP versus OP ABRs for treated bleeds by Haemophilia type for non-inhibitor cohort with routine prophylaxis at OP- MITT set

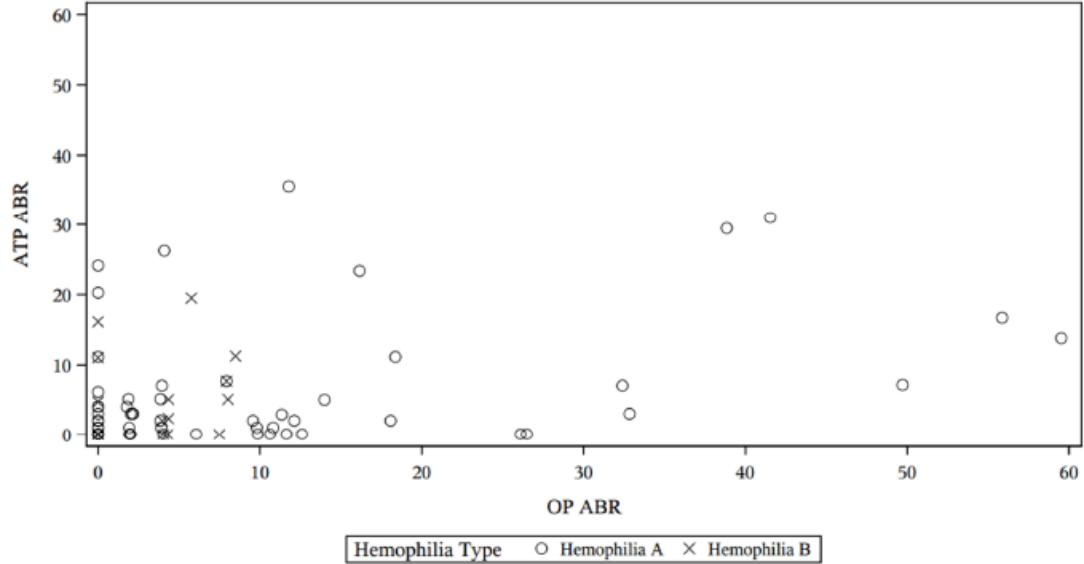
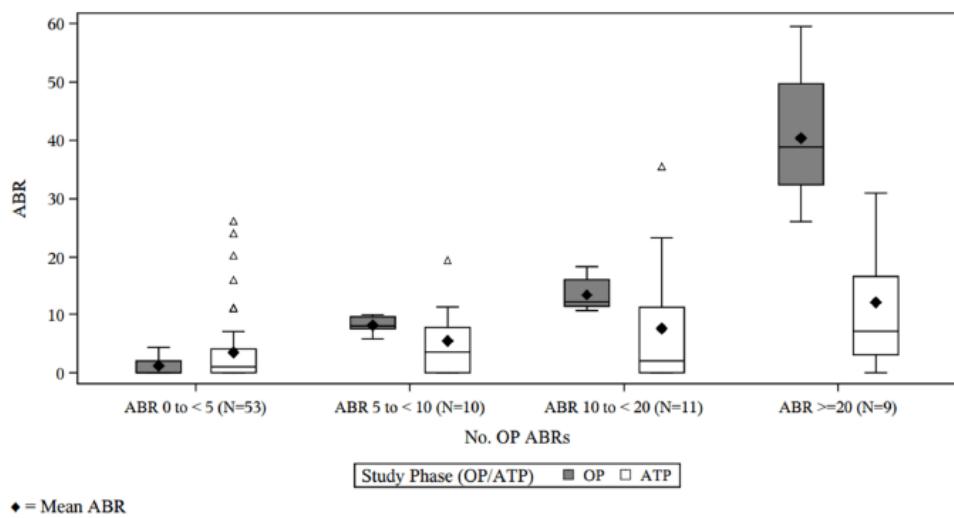


Figure 27: ABRs at OP and ATP by number of OP ABR grouping for non0inhibitor cohort with routine prophylaxis at OP – MITT set



Phase 3 OLE study B7841007

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 successfully completed the Phase 3 Study B7841005. 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 were planned to be enrolled in this study during which they would receive prophylactic treatment with marstacimab once weekly (defined as scheduled treatment by subcutaneous (SC) injection of marstacimab) at the dose established during participation in Study B7841005. The dosing regimen of marstacimab is 150 mg SC once weekly. Individual participants who meet protocol-specified dose escalation criteria based upon breakthrough bleeding in either this protocol or during participation in the earlier protocol, Study B7841005, may have the dose increased to 300 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 within each respective country between study populations with initial approvals for adolescent/adults ages 12 to <75 years, followed by the paediatric population ages 1 to <12 years. Global commercialization of marstacimab is currently anticipated to be completed in 2030, therefore the last participant's last visit in this study is estimated to be no later than 2030.

All participants were provided the pre-filled pen (PFP) for administration of marstacimab in the study. Use of the pre-filled syringe (PFS) was permitted at the investigator's discretion for those participants who had 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.

In addition, an optional, open-label, single arm, sub-study using the PFP included 23 participants rolling over from Study B7841005 who agreed to participate in the sub-study. This sub-study was implemented at the onset of treatment with marstacimab in this study with the primary objective to evaluate the feasibility and real-world effectiveness of marstacimab administration using the PFP device by the sub-study participants or their caregivers, and a secondary objective to describe difficulties experienced which resulted in unsuccessful injections, and to confirm the correct operation of the PFP by examination of returned devices.

At the time of the MAA, an interim analysis including only data from the without inhibitors cohort 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 main study.

Table 42: Study B7841007 Objectives and endpoints

Objectives	Endpoints
Primary:	Primary:
<ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> 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:
<ul style="list-style-type: none"> 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): <ul style="list-style-type: none"> 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
<ul style="list-style-type: none"> To evaluate the effect of marstacimab on HRQoL. 	<ul style="list-style-type: none"> Haem-A-QoL (≥17 years of age)/Haemo-QoL (Adolescents 12 to <17 years of age). Health Utilities Measure (EQ-5D-5L).

Number of Participants (planned and analysed):

This study was conducted at 36 sites in 14 countries: Canada (2 sites), Croatia (2 sites), France (1 site), Hong Kong (2 sites), India (2 sites), Japan (2 sites), Korea (3 sites), Mexico (1 site), Oman (2 sites), Serbia (3 sites), Spain (4 sites), Taiwan (1 site) Turkey (9 sites), and the United States (2 sites).

All 88 participants who met the eligibility criteria entered the treatment phase. Among 88 participants who entered the study, 2 discontinued from study due to withdrawal by participant, one of whom entered the follow-up phase. A total of 88 participants enrolled in the study. All 29 participants in the on-demand group were included in the safety analysis set while 58 of 59 participants in the prior prophylaxis group were included in the safety analysis set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this study were adult or adolescent male participants 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 who successfully completed the Phase 3 Study B7841005.

Duration of Study Intervention:

The study intervention marstacimab (PF-06741086) was administered on each occasion as a single 150 mg SC injection via PFS or PFP as outlined in the Instructions for Use (IFU) (unless the participant required a 300 mg dose, where 2 × 1 mL injections were used). All participants were provided the PFP for administration of marstacimab in the study. Use of the PFS was permitted at the investigator's discretion for those participants who have difficulty with administration of the PFP or for use in this study in countries where the PFS is anticipated to be the only presentation available commercially. Study staff and participants referred to the IFU for specific instructions on the handling and administration of study intervention.

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.

Only participants in the non-inhibitor cohort who completed lead-in Study B7841005 as of 10 February 2023 were included in the provided interim analysis, with a data cutoff of 10 March 2023.

Results

Study population

Disposition

All 88 participants who met the eligibility criteria entered the treatment phase. Among 88 participants who entered the study, 2 discontinued from study due to withdrawal by participant, one of whom entered the follow-up phase.

A total of 88 participants enrolled in the study. All 29 participants in the on-demand group were included in the safety analysis set while 58 of 59 participants in the prior prophylaxis group were included in the safety analysis set.

One enrolled participant from the non-inhibitor prior prophylaxis cohort is not included in the safety analysis set because his data was not available by the 10 March 2023 interim data cutoff.

Demographics and baseline characteristics

With the exception of weight, height, and eGFR, all demographic information was obtained at the parent Study B7841005 screening.

Study B7841007 was an adult and adolescent study (all participants ≥ 12 years to <75 years of age) with primarily White (43/87, 49.4%) and Asian (42/87, 48.3%) participants. There was 1 Black/African American participant (1/87, 1.1%). The race of 1 participant was not reported.

The majority of participants were from Asia (39/87, 44.8%) and Europe (30/87, 34.5%). Age was defined as the age at the time of providing informed consent at parent study (B7841005) participation.

Overall, across participants without inhibitors in Study B7841007:

- 67 (77.0%) participants had haemophilia A and 20 (23.0%) had haemophilia B
- 73 (83.9%) participants were adults ≥ 18 to <75 years of age and 14 (16.1%) of participants were adolescents (≥ 12 to <18 years of age)
- 28 (48.3%) participants with prior prophylaxis had no target joints at baseline, while all 29 (100%) participants with prior on-demand treatment had 1 or more target joints at baseline.

All 87 participants were male with a median age of 29.0 years and individual values ranged from 13.0 to 66.0 years of age. The majority of participants (54/87, 62.1%) were in the 18-44 age range.

The median participant weight was 70.4 kg (range: 39.0 to 128.8 kg) and the median participant BMI was 23.8 kg/m² (range: 15.6 to 38.9 kg/m²). The median participant height was 172.0 cm (range: 156.3 to 193.0 cm).

Most participants (68, 78.2%) had normal renal function (eGFR ≥ 90 mL/min/1.73 m²), while 14 (16.1%) had mild renal impairment (eGFR ≥ 60 to <90 mL/min/1.73 m²) and none had moderate renal impairment (eGFR ≥ 30 to <60 mL/min/1.73 m²).

Efficacy results

ABR of treated bleeds

The long-term efficacy of marstacimab administered beyond 12 months in parent Study B7841005 and up to an additional approximately 16 months in participants without inhibitors as measured by the ABR of treated bleeds was maintained in this long-term extension study.

Overall, the model-based mean estimated ABR of treated bleeds was 2.79 and the 95% CI was (1.90, 4.09).

For the prior on-demand group, the model-based mean estimated ABR of treated bleeds was 3.86 and the 95% CI was (2.02, 7.37). For the prior prophylaxis group, the estimated ABR of treated bleeds was 2.27 and the 95% CI was (1.40, 3.67).

Overall, 49 of 87 participants had no bleeding events over the treatment period ranging from 34.0 to 483.0 days, with a median exposure of 193.0 days. Over the treatment period, in the prior on-demand group 13 of 29 participants had no bleeding events and in the prior prophylaxis group, 36 of 58 participants had no bleeding events.

Incidence of joint bleeds

The long-term efficacy of marstacimab in participants without inhibitors, as measured by the incidence of joint bleeds, beyond 12 months in parent Study B7841005 and up to an additional approximately 16 months was maintained in the long-term OLE Study B7841007.

The overall model-based mean estimate for the annualised incidence of joint bleeds was 1.88 (95% CI [1.29, 2.74]), and for the prior on-demand group and prior prophylaxis group was 1.87 (95% CI [1.07, 3.26]) and 1.87 (95% CI [1.14, 3.08]), respectively.

Incidence of spontaneous bleeds

The long-term efficacy of marstacimab in participants without inhibitors, as measured by the incidence of spontaneous bleeds, beyond 12 months in parent Study B7841005 and up to an additional approximately 16 months was maintained in long-term OLE Study B7841007.

The overall model-based mean estimate for the annualised incidence of spontaneous bleeds was 1.91 (95% CI [1.26, 2.89]), and for the prior on-demand group and prior prophylaxis group was 2.54 (95% CI [1.22, 5.29]) and 1.62 (95% CI [0.96, 2.73]), respectively.

Incidence of target joint bleeds

The long-term efficacy of marstacimab in participants without inhibitors, as measured by the incidence of target bleeds, beyond 12 months in parent Study B7841005 and up to an additional approximately 16 months was maintained in long-term OLE Study B7841007.

The overall model-based mean estimate for the annualised incidence of target joint bleeds was 0.94 (95% CI [0.54, 1.63]), and for the prior on-demand group and prior prophylaxis group was 0.90 (95% CI [0.51, 1.58]) and 0.91 (95% CI [0.36, 2.27]), respectively.

Incidence of total bleeds (treated and untreated)

The long-term efficacy of marstacimab in participants without inhibitors beyond 12 months in parent Study B7841005 and up to an additional approximately 16 months as measured by the incidence of total bleeds (treated and untreated), was maintained in long-term OLE Study B7841007.

The overall model based mean estimate for the annualised incidence of total bleeds (treated and untreated) was 3.59 (95% CI [2.56, 5.04]), and for the prior on-demand group and prior prophylaxis group was 5.10 (95% CI [3.25, 8.00]) and 2.73 (95% CI [1.70, 4.38]), respectively.

Haemophilia Joint Health Score (HJHS)

Marstacimab prophylaxis preserved joint health as assessed by the HJHS in participants without inhibitors who contributed Day 180 HJHS values by the interim data cutoff.

A lower HJHS value is indicative of better joint health.

The mean change from Study B7841007 baseline at 180 days in the total HJHS score was -1.0 across all participants (n=43 with values reported at 180 days).

For the prior on-demand group (n=19) and the prior prophylaxis group (n=24), the mean change from Study B7841007 baseline in the total HJHS score at 180 days was 1.1 and -2.7, 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 approximately 16 months was maintained in long-term OLE Study B7841007 in participants without inhibitors.

A target joint is defined as a major joint (eg, 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). The number of target joints is derived from the eDiary via counting joints that meet the definition of a target joint during the treatment period.

The overall mean for the number of target joints was 0.09. For the prior on-demand group and prior prophylaxis group, the mean was 0.07 and 0.10, respectively.

Total coagulation factor consumption

The mean total IU (annualised) factor replacement consumption was 9954.9, and for the prior on-demand group and prior prophylaxis group was 14807.1 and 7528.8, respectively, in participants without inhibitors.

HRQoL outcomes

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

The treatment effect with marstacimab prophylaxis in the physical health domain and total scores in the Haem-A-QoL and Haemo-QoL instrument was preserved with long-term treatment in this study in participants without inhibitors who contributed Day 180 values by the interim data cutoff.

Participants who turned 17 years of age at Study B7841007 rollover and became newly eligible to fill out the Haem-A-QoL did so at Study B7841007 baseline. Participants who aged into a new version of the questionnaire in a given year completed the age-appropriate version of the questionnaire.

A lower Haem-A-QoL/Haemo-QoL physical health domain or total score is indicative of a better quality of life.

For the Haem-A-QoL, across all participants who reported values at 180 days (n=42), the mean change from Study B7841007 baseline at 180 days in the physical health domain and total scores was -0.7 and -0.2, respectively. For the prior on-demand group, across participants who reported values at 180 days (n=18) the mean change from Study B7841007 baseline at 180 days in the physical health domain and total scores was -3.2 and -2.0, respectively. For the prior prophylaxis group, across participants who reported values at 180 days (n=24), the mean change from Study B7841007 baseline at 180 days in physical health domain and total score was 1.1 and 1.1, respectively.

For the Haemo-QoL, a total of n=3 participants reported physical health domain and total scores at 180 days, all from the prior prophylaxis group. The mean change from Study B7841007 baseline at 180 days in the physical health domain and total scores was -4.8 and -3.5, respectively.

EQ-5D-5L

The treatment effect with marstacimab prophylaxis in the EQ-5D-5L index and EQ-VAS scores was preserved with long term treatment in this study in participants without inhibitors who contributed Day 180 values by the interim data cutoff.

A higher value in the EQ-5D-5L index score and EQ-VAS score is indicative of a better health state.

Across all participants who contributed Day 180 values, (n=44), the mean change from Study B7841007 baseline at 180 days in the index score was 0.0. Across all participants who contributed Day 180 values (n=46), the mean change from Study B7841007 baseline at 180 days in the EQ-VAS score was -1.8.

For prior on-demand group participants who contributed Day 180 values (n=18), the mean change at Study B7841007 baseline at 180 days in the index score was 0.0, while the mean change in the EQ-VAS score (n=19) was -1.4.

For prior prophylaxis group participants who contributed Day 180 values (n=26), the mean change at Study B7841007 baseline at 180 days in the index score was 0.0, while the mean change in the EQ-VAS score (n=27) was -2.1.

Phase 3 OLE Sub-study of B7841007

This was an optional, open-label, single arm sub-study for adult or adolescent haemophilia A or B participants enrolled in the Phase 3 open-label clinical Study B7841007 who agreed to participate in the sub-study. All eligible participants had successfully completed participation in the Phase 3 B7841005 parent study, where marstacimab was administered using a prefilled syringe (PFS) format. This sub-study was implemented at the onset of treatment with marstacimab in this study to evaluate whether sub-study participants or their caregivers could effectively administer marstacimab using the sponsor's PFP device. Approximately 20 study participants were planned to be enrolled and dosed in this sub-study. Participants signed consent for the sub-study at the Study B7841007 Baseline Visit or during the "Study Completion" visit in the B7841005 study. The sub-study participants continued to follow all the main study procedures.

The number of injections and corresponding assessments during the sub-study depended on the dose of marstacimab that the participant was prescribed in Study B7841005, either 150 mg subcutaneously (SC) once weekly or 300 mg SC once weekly (300 mg = 2 × 150 mg injections administered a few minutes apart in different body sites). Participants (or their caregiver if applicable) were to administer up to 6 consecutive weekly doses of marstacimab as tolerated, using the PFP device. The 1st, 3rd, and 6th injections for participants prescribed 150 mg SC and the 1st/2nd, 5th/6th, and 11th/12th injections for participants prescribed 300 mg SC were to be administered at the site under the supervision of the investigator or designated observer. These visits were additional visits for sub-study participants. Participants or their caregiver were to administer their marstacimab dose using the PFP at home for all other injections during the sub-study.

An assessment of participant's acceptability of marstacimab injections with the PFP was to be performed by the participant or caregiver (person administering the PFP) using the PAT within 10 minutes after each PFP injection during sub-study participation throughout the 6-week sub-study period from all participants who had at least 1 attempted administration of study intervention using the PFP device.

An assessment of participant's useability of marstacimab injections with the PFP was to be performed by the investigator or designated observer using the OAT within 10 minutes after the PFP injection at Sub-

study Weeks 1, 3, and 6 during sub-study participation from all participants who had at least 1 attempted administration of study intervention using the PFP device.

The sub-study participants were required to properly retain and return all used PFPs and any unused PFPs with issues potentially preventing normal function, to support a post-study mechanical evaluation of the PFP devices.

Additional medical history for all sub-study participants was obtained, including bilateral hand or wrist disability by report (carpal tunnel, proximal/distal interphalangeal flexion contracture/hyperextension, tendon rupture, joint replacement, or joint fusion).

Sub-study participants who signed informed consent but never attempted injection with the PFP on Sub-study Day 1 were to be replaced so as to ensure a sample size of approximately 20 participants. Sub-study participants who attempted injection with the PFP on Sub-study Day 1 but did not succeed were not to be replaced; however, an additional participant was to be enrolled to supplement the exposure and PFP performance data for participants receiving at least one injection by PFP.

If the sub-study participant was consistently unable to use the PFP following instruction and observation, the participant would be discontinued from the sub-study and would return to using the PFS for the remainder of their participation in the main study. Following completion of the sub-study, all participants were to continue use of the PFP for the remainder of the main Study B7841007.

Number of Participants (planned and analysed):

This sub-study was conducted at 11 sites in 4 countries: Hong Kong (2 sites), India (2 sites), Republic of Korea (1 site), and Turkey (6 sites). All sub-study participants from these sites were the earliest participants to transition from the parent Study B7841005.

A total of 23 participants were screened after signing a sub-study informed consent document (ICD), all of whom entered the sub-study and received treatment with marstacimab using the PFP device. All 23 treated participants completed the sub-study.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Enrolled in this sub-study were a subset of the main Study B7841007 adult or adolescent participants with severe haemophilia A or moderately severe to severe haemophilia B (rolled over from the parent Study B7841005), who consented to participate in the PFP sub-study.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

The study intervention marstacimab (PF-06741086) was provided in a sterile liquid solution for injection packaged in a PFP for single use, which contained a standard marstacimab PFS. Each package was labelled as required per country requirement. Study intervention information is provided in the table below.

Table 43: Study intervention(s) administered

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-06741086 Solution for Injection, 150 mg/mL prefilled pen	ET2299	21-DP-00515	150 mg/mL	Solution

Duration of Study Intervention:

Marstacimab was administered on each occasion as a single 150 mg SC injection (unless the participant required 300 mg dose, where 2 x 150 mg injections would be used). Study intervention was to be injected either into the abdominal wall or upper front thigh. The participant or trained caregiver were to utilise both injection locations during the sub-study.

If a participant or trained caregiver failed the first injection attempt at any injection week, the participant or trained caregiver was allowed to make a second attempt only if the full dose was not administered, starting with a new PFP device.

If a participant or trained caregiver was unable to physically use the device and inject using the PFP on sub-study Day 1 (eg, could not remove the cap, could not exert sufficient force to initiate the injection, etc), even with repeated assistance and attempts, then the Observer and Participant Assessment tools were to be completed, the participant would be discontinued from the sub-study, and their data would be included in the analysis. The participant was to return to administration of their study treatment using the PFS for the remainder of their participation in the main Study B7841007.

All PFPs that were used in the sub-study and all PFPs that were the subject of a Medical Device Complaint record were to be returned to the sponsor for analysis. The PFP was defined as the pen and its cap, whether the cap had been removed or not. Once the cap had been removed, no attempt was to be made to replace it on the pen. All used PFPs (and their caps) were to be immediately placed in the sponsor-supplied individual biohazard disposal containers for secure storage.

For all such defined PFPs that were administered at a participant's home, site personnel instructed the participant to store the PFPs, as described, until they could be returned to the site for return to the sponsor. For all such defined PFPs that had been administered at the site, site personnel were responsible for ensuring their correct storage until they could be returned to the sponsor. Instructions for returning all such defined PFPs were provided to the sites by the sponsor and/or designee.

Table 44: Sub study objectives and endpoints

	Objective	Endpoint
Primary	To evaluate the feasibility and real-world effectiveness of marstacimab administration by the participant with hemophilia or their caregiver using the PFP device.	Delivery system success rate (DSSR) based on participant (actual PFP user, either participant or participant's caregiver) and investigator/designated observer observations of the success of marstacimab administration by PFP.
Secondary	<p>To describe the difficulties experienced which resulted in unsuccessful injections of marstacimab by the participant or their caregiver using the PFP device.</p> <p>To confirm the correct operation of the marstacimab PFP by examination of returned devices.</p>	<p>Characterization of unsuccessful PFP injections.</p> <p>Determination, by inspection, of the correct mechanical function of returned PFP devices.</p>

Analysis Sets

Sub-study Intent-to-Treat (ITT) Analysis Set: Sub-study participants who attempted to take at least one dose (150 mg or 300 mg) of marstacimab using the PFP device.

Sub-study Safety Analysis Set: Sub-study participants who received at least a portion of a dose of marstacimab using the PFP device.

Analysis of the Primary Endpoint

The primary sub-study endpoint was DSSR, which was based on participant (actual PFP user, either participant or participant's caregiver) and investigator/designated observer observations of the success of marstacimab administration by PFP.

Delivery success was based on a lack of injection failure reported on the participant assessment tool (PAT), as described below:

- Question 3 "Do you believe a full dose was injected?":
 - A "No" response indicated injection failure.
- Question 4 "Did the yellow bar on the pen move across the window as shown below?":
 - A "No" response indicated injection failure.
- Question 5 "Did you have any difficulties during the injection?":
 - A "Yes" response with the difficulty option selected, "Medicine was still flowing out of the pen after it was removed from the skin," indicated injection failure.

Note: A "Yes" response to Question 5 with the following difficulty options selected was not an indication of injection failure:

- I had trouble removing the cap.

- I had trouble starting the injection.
- I did not hear the 2nd click before removal of the pen from the skin.

When the observer assessment tool (OAT) was available, delivery success was also based on a lack of injection failure reported on the OAT, as described below:

- Question 2 "Did the user successfully self-administer the full dose without physical assistance?":
 - A "No" response indicated injection failure.

In order to consider "injection success", delivery of the entire dose (ie, whether 1 × 150 mg PFP required for 150 mg dose; or 2 × 150 mg PFP required for 300 mg dose) must have been measured as "success" at any injection timepoint/sub-study visit. That is, the DSSR per visit for participants who received 300 mg was to be treated as a composite endpoint, where both the first and second injections needed to meet the criteria for 'success' to be determined successful for the DSSR. If any injection during a visit was a 'failure', this was to be considered a participant failure for the DSSR at this visit.

Analysis of Secondary Endpoints

- Characterisation of unsuccessful PFP injections was descriptive and based on individual question responses to PAT and OAT.
- Individual question responses to PAT/OAT were summarised by PFP injection visit using counts and percentages.
- Determination, by inspection, of the correct mechanical function of returned PFP devices was described in a separate mechanical report.

Results

Demographic and Other Baseline Characteristics:

All 23 participants were male. The median participant age was 25 years and individual values ranged from 14 to 44 years. The majority of participants (19/23, 82.6%) were in the 18-44 years age range. All 23 participants were of Asian (15/23, 65.2%) or White (8/23, 34.8%) race.

The median participant weight was 67.0 kg (range: 38.1 to 99.8 kg) and the median participant body mass index (BMI) was 22.4 kg/m² (range: 15.2-35.3 kg/m²). The median participant height was 169.0 cm (range: 158.0-178.0 cm).

Of the 23 treated sub-study participants, 20 (87.0%) participants had haemophilia A (16 adult and 4 adolescent participants), and 3 (13.0%) participants had haemophilia B (3 adult and 0 adolescent participants). Participant median number of bleeds in the past 6 months prior to entry into pivotal Study B7841005 was 15 bleeds; individual values ranged from 0 to 85 bleeds, with the majority of participants (21 [91.3%]) having 6 or more bleeds in the past 6 months. The majority of participants had 1 or more target joints at baseline.

Exposure:

Of the 23 total sub-study participants, 20 participants were prescribed marstacimab treatment at a dose of 150 mg SC weekly and 3 participants were prescribed marstacimab treatment at a dose of 300 mg SC weekly.

Among sub-study participants, the median duration of marstacimab treatment within the sub-study period was 42 days (range: 35 to 45 days) and the median exposure days of marstacimab treatment was 6 days (range: 5 to 6 days).

PFP Device Injection Success Evaluation Results:

- The DSSR was 100% at all visits except for Week 2, which had a DSSR of 95.0%, with an overall DSSR across all visits of 99.2%. The overall DSSR was based on 123 delivery system success assessments, of which 122 were considered successful.
 - The inspection of 156 used PFPs returned per the administration schedule, confirmed successful injection of the full contents from the syringe for all returned used PFPs.
 - The following issues were identified for 1 PFP injection attempt noted by the actual PFP User (PAT): “trouble starting the injection” and “medicine still flowing after pen removed from the skin.”
 - The following issues were identified for 2 PFP injection attempts noted by the OAT: the user did not successfully self-administer the full dose without physical and verbal assistance due to both participants asking a healthcare professional to administer for them. The following issue was identified for 1 PFP injection attempt noted by the OAT: the user did not successfully self-administer the full dose without verbal assistance due to needing help with Step 7, “Inject Medicine.”
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- **Summary of main efficacy results**

The following tables 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 45: Summary of efficacy for trial B7841005

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):	6 months
	Duration of Active Treatment Phase (ATP):	12 months
	Duration of follow-up:	1 month follow-up for safety monitoring

Efficacy data presented in the initial MAA includes only the completed non-inhibitor cohort; no efficacy data is included in the initial MAA for the ongoing inhibitor cohort.

Hypothesis	<p>Non-Inhibitor Cohort</p> <p>Non-inferiority, and superiority if non-inferiority is met, of marstacimab prophylaxis during the active treatment phase (ATP) as compared to prior prophylaxis during the observational phase (OP), and superiority of marstacimab prophylaxis over on-demand factor replacement during the OP.</p>		
Treatment groups	Marstacimab (PF-06741086)	<p>12-month Active Treatment Phase following a 6-month Observational Phase: Marstacimab administered 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</p> <p>Treatment for the 6-month observational phase was divided into 2 cohorts:</p> <ul style="list-style-type: none"> Non-inhibitor cohort: participants without inhibitors who had prior on-demand or prior prophylaxis factor-based therapy Inhibitor cohort: participants with inhibitors who were receiving prior on-demand treatment 	
Endpoints and definitions	Primary Endpoint	ABR of treated bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for: non-inferiority versus prior prophylaxis and superiority versus prior prophylaxis. In addition, superiority versus on-demand was tested outside of the testing hierarchy.
	Secondary Endpoint	Incidence of joint bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for: non-inferiority versus prior prophylaxis and superiority versus prior prophylaxis. In addition, superiority versus on-demand was tested outside of the testing hierarchy.
	Secondary Endpoint	Incidence of spontaneous bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for: non-inferiority versus prior

			prophylaxis and superiority versus prior prophylaxis. In addition, superiority versus on-demand was tested.
	Secondary Endpoint	Incidence of target joint bleeds	Statistical testing was conducted for marstacimab based on prespecified ordering for: non-inferiority versus prior prophylaxis and superiority versus prior prophylaxis. In addition, superiority versus on-demand was tested.
	Secondary Endpoint	Incidence of total bleeds (treated and untreated)	Statistical testing was conducted for marstacimab based on prespecified ordering for: non-inferiority versus prior prophylaxis and superiority versus prior prophylaxis. In addition, superiority versus on-demand was tested.
	Secondary Endpoint	Change in joints as measured by the Haemophilia Joint Health Score (HJHS)	The change from baseline in the total score was measured at 6 months in the ATP versus during the 6-month OP. The HJHS total score is not included in the testing hierarchy where type I error rate is controlled within each statistical objective.
Data Cutoff Date (LPLV for non-inhibitor cohort)	17 April 2023 (interim analysis for non-inhibitor cohort)		
<p>Results and Analysis</p> <p>Marstacimab prophylaxis demonstrated non-inferiority and superiority (2-sided p-value =0.0376) over routine prophylactic treatment as measured by the ABR of treated bleeds. Marstacimab prophylaxis also demonstrated superiority (2-sided p-value <0.0001) over on-demand treatment as measured by the ABR of treated bleeds. Marstacimab prophylaxis demonstrated non-inferiority over prior prophylactic treatment and superiority over on-demand treatment and reduced the incidence of the following types of bleeds as compared to both on-demand and prior prophylactic treatment: joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds (treated and untreated).</p> <p>Marstacimab prophylaxis demonstrated non-inferiority when compared with prior routine prophylaxis for Haem-A-QoL physical health domain and total score, and EQ-5D-5L index score and EQ-VAS score.</p>			
Analysis description	<p>Primary Analysis: ABR of treated bleeds</p> <p>Analysis population and time point description</p> <p>Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab during the ATP.</p>		

Descriptive statistics and estimate variability	Treatment group	Marstacimab			
	Number of participants	116			
	Mean estimated ABR (95% CI; p value)	Prior On-Demand (n=33) ATP: 3.18 (2.09, 4.85; p<0.0001) OP: 38.00 (31.03, 46.54)	Prior Prophylaxis (n=83) ATP: 5.08 (3.40, 6.77; p = 0.0376) OP: 7.85 (5.09, 10.61)		
	ABR Ratio (95% CI)	0.084 (0.059, 0.119)	NA		
	Difference estimate (95% CI)	NA	-2.77 (-5.37, -0.16)		
	Percentage reduction (95% CI)	NA	35.2% (5.6, 55.6)		
	Participants without treated bleeds (%)	ATP: 10 (30.3%) OP: 1 (3.0%)	ATP: 29 (34.9%) OP: 33 (39.8%)		
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand or prophylactic factor 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.				
Descriptive statistics and estimate variability	Treatment group	Marstacimab			
	Number of participants	116			
	Mean estimate (95% CI)	Prior On-Demand (n=33) ATP: 2.83 (1.81, 4.44) OP: 32.86 (26.15, 41.29)	Prior Prophylaxis (n=83) ATP: 4.13 (2.59, 5.67) OP: 5.66 (3.33, 7.98)		
	Ratio estimate (95% CI)	0.086 (0.059, 0.125; p <0.0001)	NA		
	Difference estimate (95% CI)	NA	-1.53 (-3.70, 0.64) Non-inferiority margin: upper bound of 95% CI <2.5		
	Participants without treated joint bleeds (%)	ATP: 10 (30.3%) OP: 1 (3.0%)	ATP: 33 (39.8%) OP: 40 (48.2%)		
	Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand or prophylactic factor treatment			
Analysis description	Secondary analysis: incidence of spontaneous bleeds				
Analysis population and time	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP.				

point description			
Descriptive statistics and estimate variability	Treatment group	Marstacimab	
	Number of participants	116	
	Mean estimate (95% CI)	Prior On-Demand (n=33)	Prior Prophylaxis (n=83)
		ATP: 2.44 (1.61, 3.69) OP: 30.93 (24.12, 39.67)	ATP: 3.78 (2.25, 5.31) OP: 5.86 (3.54, 8.19)
	Ratio estimate (95% CI)	0.079 (0.054, 0.114; p <0.0001)	NA
	Difference estimate (95% CI)	NA	-2.09 (-4.23, 0.06) Non-inferiority margin: upper bound of 95% CI <2.5
	Participants without spontaneous bleeds (%)	ATP: 10 (30.3%) OP: 2 (6.1)	ATP: 35 (42.2%) OP: 40 (48.2%)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand or prophylactic factor treatment.		
Analysis description	Secondary analysis: incidence of target joint bleeds (treated)		
Analysis population and time point description	Modified intent-to-treat (mITT): participants without inhibitors who completed the OP and received at least 1 dose of marstacimab in the ATP.		
Descriptive statistics and estimate variability	Treatment group	Marstacimab	
	Number of participants	As indicated below	
	Mean estimate (95% CI)	Prior On-Demand (n=33)	Prior Prophylaxis (n=83)
		ATP: 1.84 (1.06, 3.17) OP: 23.18 (17.20, 31.24)	ATP: 2.51 (1.25, 3.76) OP: 3.36 (1.59, 5.14)
	Ratio estimate (95% CI)	0.079 (0.051, 0.124); p <0.0001	NA
	Difference estimate (95% CI)	NA	-0.86 (-2.41, 0.70) Non-inferiority margin: upper bound of 95% CI <1.2
	Participants without any bleeds (treated) (%)	ATP: 13 (39.4%) OP: 2 (6.1%)	ATP: 54 (65.1%) OP: 62 (74.7%)
Effect estimate per comparison	Post marstacimab administration for 12 months in the ATP versus the 6-month OP with on-demand or prophylactic factor treatment.		
Analysis description	Secondary analysis: incidence of total bleeds (treated and untreated)		
Analysis population and time	Modified intent-to-treat (mITT): participants who completed the OP and received at least 1 dose of marstacimab in the ATP.		

point description			
Descriptive statistics and estimate variability	Treatment group	Marstacimab	
	Number of participants	As indicated below	
		Prior On-Demand (n=33)	Prior Prophylaxis (n=83)
	Mean estimate (95% CI)	ATP: 7.39 (5.08, 10.74) OP: 47.76 (39.60, 57.60)	ATP: 5.97 (4.13, 7.81) OP: 8.84 (5.97, 11.72)
	Ratio estimate (95% CI)	0.155 (0.116, 0.207; p <0.0001)	NA
	Difference estimate (95% CI)	NA	-2.87 (-5.61, -0.12) Non-inferiority margin: upper bound of 95% CI <2.9
	Participants without any bleeds (treated and untreated) (%)	ATP: 4 (12.1%) OP: 0 (0.0%)	ATP: 22 (26.5%) OP: 28 (33.7%)
Effect estimate per comparison	Post marstacimab administration for 12 months versus the 6-month OP with on-demand or prophylactic factor treatment.		
Analysis description	Secondary analysis: HJHS		
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. 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 ATP is at 6 months, and the 12-month comparison utilises 6-month results from the OP.		
Descriptive statistics and estimate variability	Treatment group	Marstacimab	
	Number of participants	As indicated below	
		Prior On-Demand (n=33)	Prior Prophylaxis (n=83)
	Median estimate change in total score from baseline to 6 months (95% CI)	ATP: -5.2 (-8.7, -1.8) OP: -2.6 (-5.7, 0.5)	ATP: -0.6 (-2.2, 1.0) OP: 1.3 (-0.7, 3.3)
	Estimated median difference (95% CI)	-2.8 (-7.6, 2.1)	-2.0 (-4.3, 0.3)
Effect estimate per comparison	Post marstacimab administration at 6 months in the ATP versus the 6-month OP with on-demand or prophylactic factor treatment.		

2.6.5.3. Clinical studies in special populations

No studies were performed investigating Hympavzi in special populations.

Currently available efficacy data are limited to patients ≥ 12 years of age. Efficacy data from elderly patients are very limited with only 1 patient ≥ 65 years of age.

Marstacimab has not been studied in patients with moderate or severe hepatic or renal impairment.

2.6.5.4. *In vitro biomarker test for patient selection for efficacy*

Not applicable.

2.6.5.5. *Analysis performed across trials (pooled analyses and meta-analysis)*

Not applicable.

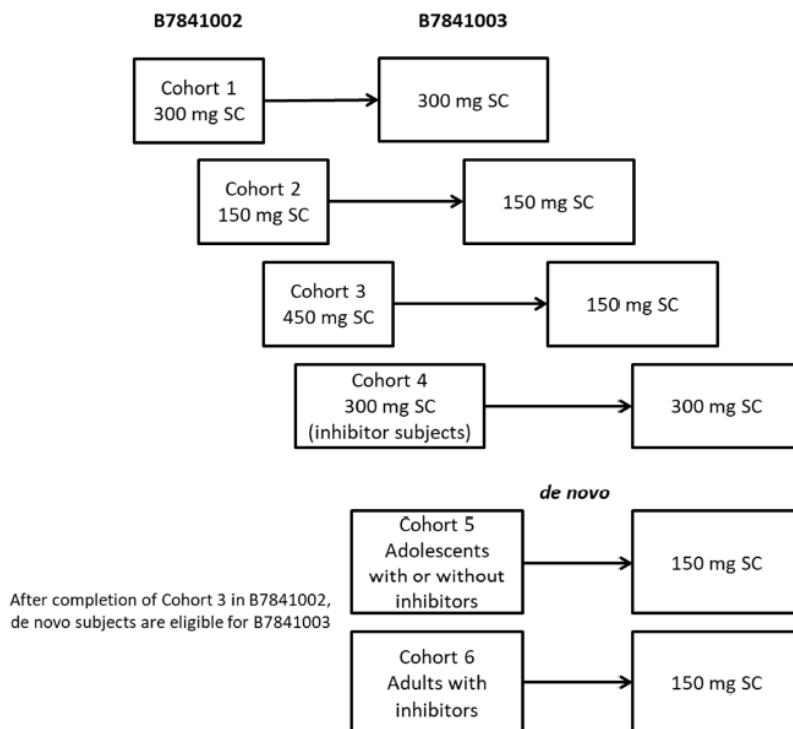
2.6.5.6. *Supportive study(ies)*

B7841003: Phase 2 OLE Study

Study B7841003 was an open-label long-term (treatment of up to 365 days) evaluation of marstacimab as a prophylactic treatment regimen in participants with severe haemophilia A or B, with or without inhibitors to FVIII or FIX.

Approximately 36 participants (24 participants from Study B7841002 and 12 additional participants not previously enrolled in a study) were planned for enrollment at approximately 20 study sites. Participants who enrolled in Study B7841003 from Cohort 1 or 4 (marstacimab 300 mg SC of Study B7841002 participants with and without inhibitors) continued with their assigned dose level at the completion of Study B7841002. All other participants enrolled in Study B7841003 received 150 mg SC, the lowest dose level determined to be safe and efficacious in Study B7841002. All participants who successfully completed Study B7841002 were eligible for enrollment into Study B7841003.

Figure 28: B7841003 Dose assignment



Efficacy Results

18 participants were previously enrolled in B7841002 and 2 adult participants with inhibitors were newly enrolled. Among these 20 participants, all were treated with marstacimab and 18 participants completed the study.

The table below shows that across all dose cohorts during this study, the mean and median on-study ABR ranged from 0 to 3.586 and 0 to 2.488 bleeding episodes per participant per year, respectively, demonstrating comparable efficacy observed in the short-term parent Study 1002.

Out of the 20 participants in Study 1003, there was 1 participant with haemophilia B from the 300 mg loading + 150 mg – 300 mg loading + 150 mg non-inhibitor dose cohort, who completed the study and had no bleeding events during the study.

There was a numerical reduction in ABR in the on-study treatment phase versus that reported for the pre-treatment (pre-study) phase in all dose cohorts.

Table 46: PF-06741086 Protocol B7841003 descriptive summary of annualised bleeding rate by dose cohort in B7841003 - PPAS

Study Phase	Summary Statistics	300mg - 300mg Non-Inhibitor (N = 5)	300mg Loading + 150mg Non-Inhibitor (N = 4)	450mg - 300mg Loading + 150mg Non-Inhibitor (N = 4)	300mg - 300mg Inhibitor (N = 5)	De Novo 300mg Loading + 150mg Inhibitors (N = 2)	Overall - 300mg (N = 10)	Overall - 300mg Loading + 150mg (N = 10)
		n	n	n	n	n	n	n
Pre-Treatment ^a	n	5	4	4	5	2	10	10
	Mean	22.000	14.000	22.000	18.400	15.000	20.200	17.400
	SD	7.8740	1.6330	13.5647	1.6733	4.2426	5.6921	8.9468
	Median	20.000	14.000	17.000	18.000	15.000	19.000	15.000
	(Q1, Q3)	(18.00, 30.00)	(13.00, 15.00)	(14.00, 30.00)	(18.00, 20.00)	(12.00, 18.00)	(18.00, 20.00)	(12.00, 18.00)
	Min	12.00	12.00	12.00	16.00	12.00	12.00	12.00
	Max	30.00	16.00	42.00	20.00	18.00	30.00	42.00
On-Study	n	5	4	4	5	2	10	10
	Mean	2.971	3.586	1.916	0.000	2.488	1.486	2.699
	SD	2.7895	7.1726	1.4492	0.0000	3.5187	2.4312	4.4561
	Median	2.029	0.000	2.077	0.000	2.488	0.000	0.977
	(Q1, Q3)	(0.98, 5.86)	(0.00, 7.17)	(0.98, 2.86)	(0.00, 0.00)	(0.00, 4.98)	(0.00, 2.03)	(0.00, 3.51)
	Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Max	5.99	14.35	3.51	0.00	4.98	5.99	14.35

Safety analysis set was defined as all participants who received at least one dose of study medication in B7841003.

Per protocol analysis set (PPAS) was a subset of the safety analysis set, this set excluded participants with major protocol deviations. For one participant who had 62 days of dosing gap and then 90 days of dosing gap due to knee replacement after 2 doses, only the portion of data before the first dosing gap was included.

a. Pre-Treatment summarized the data up to 6 months prior to participation in B7841003 for de novo participants and up to 6 months prior to participation in B7841002 for rollover participants.

2.6.6. Discussion on clinical efficacy

The intended indication for Hympavzi is 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.

Efficacy data are available from 4 clinical studies: single pivotal Phase 3 study B7841005 with two completed non-inhibitor cohorts, Phase 3 OLE study B7841007, Phase 1b/2 study B7841002 and Phase 2 OLE study B7841003.

The pivotal clinical efficacy results are derived from the Phase 3 study B7841005 and its OLE study B7841007. Data from the Phase 1b/2 study B7841002 and its OLE study B7841003 are considered supportive evidence.

Design and conduct of clinical studies

Pivotal Study B7841005

Study B7841005 is a one-way, cross-over, open-label, multi-centre study planned for approximately 145 adolescent and adult participants between 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 inhibitor, with approximately 20% of participants as adolescents (ages between 12 to <18 years old). Participants were to be enrolled into either an inhibitor cohort (currently ongoing, no data available at this time) or into a non-inhibitor cohort (completed). For the haemophilia B study population, initially only patients with severe disease phenotype were eligible for enrolment, which was changed via amendment of the study protocol due to slow recruitment progress. It is noted that only 1 HB patient with moderately severe disease was included in the study and therefore no conclusions on efficacy in this patient population can be made. This however is of no concern, as only an indication for severe haemophilia B is applied for.

The study duration for an individual participant is approximately 21 months, which includes a 45-day screening period, a 6-month observational phase (on-demand or routine prophylactic treatment), 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.

HA and HB are rare diseases which causes limitations in patient availability for clinical studies. Moreover, haemophilia patients are heterogeneous with regards to clinical signs and symptoms, such as bleeding phenotype, bleeding risk due to different lifestyle and individual treatment history, target joints, risk for inhibitors etc. In consequence, feasibility of sufficiently informative, randomised, controlled trials to estimate efficacy and safety of a novel therapeutic agent is challenging in this disease setting. While a randomised-controlled study would be the preferred option, conduct of a single arm study with an intra-participant comparison relative to a prospectively captured baseline is considered acceptable. The duration of the active treatment phase of 12 months is acceptable and the overall design is in line with guidance (EMA/HAEMWP/136018/2023; currently in draft stage) and previous SA.

Important protocol deviations were reported for 74 (57.8%) participants in study B7841005. Most deviations were reported related to procedures/tests (31 participants), investigational product (25 participants), concomitant medications (22 participants), informed consent (18 participants), and inclusion/exclusion criteria (10 participants).

For the EU, and specifically for the non-inhibitor cohort, the statistical hypothesis was the demonstration of non-inferiority of Hympavzi prophylaxis observed over the 12-month ATP compared to routine prophylaxis during the 6 months prior to receiving study intervention (i.e. the prospectively conducted observational period), on the difference in the ABR of treated bleeds. The statistical hypothesis of establishing non-inferiority against routine prophylaxis is considered the appropriate comparison for the non-inhibitor cohort. Additionally, superiority testing was specified for the comparison of marstacimab prophylaxis compared to previous on-demand factor treatment during the observational period, which is considered supportive evidence.

Primary endpoints

The primary endpoint was the annualised bleeding rate (ABR) of treated bleeding events over a 12-month Active Treatment Phase (ATP) compared to a previous 6-month Observational Phase (OP), which is in line with scientific advice and in line with guidance. The primary endpoint is clinically relevant and clearly defined. While a within subject comparison between the on-treatment duration and the prior observational period has a risk for bias, the strategy is acceptable in this rare disease. A non-inferiority margin of 2.5 was pre-specified. Regarding its derivation it is unclear in how far the study populations investigated in the three studies used for the non-inferiority margin derivation are comparable to the study population in the pivotal marstacimab study B7841005. This is especially the case for the two included HB Benefix studies, where moderately severe and severe HB patients were enrolled, whereas the HB study population in B7841005 was almost exclusively made up of HB patients with severe disease and a severe phenotype. Further, no justification of the clinical irrelevance of 2.5 additional treated bleeding events per year was provided in the dossier. However, since in addition to non-inferiority also superiority of marstacimab prophylaxis over routine prophylaxis was demonstrated for the primary analysis, these issues are not further pursued.

The primary analysis was supplemented with prospectively defined sensitivity analyses aiming to investigate the impact of preventative infusions, marstacimab dose escalation (by including data after dose escalation into the analysis), treatment discontinuation, carryover effect from OP to ATP (by excluding data from the first month of marstacimab treatment), and seasonal effects (by including only the portion of ATP into the analysis that match the calendar time of the OP). These sensitivity analyses are considered to provide important additional insight into the generated efficacy data and are acceptable.

Secondary endpoints

Secondary endpoints included bleeding rates for different bleeding events, including incidences of joint bleeds, spontaneous bleeds, target joint bleeds, and total (treated and untreated) bleeds. These secondary endpoints based on bleeding rates provide additional clinically relevant data and supplement the primary endpoint. They are in line with guidance and previously provided EMA scientific advice.

Additional secondary endpoints include Haemophilia joint health score and PROs Haem-A-QoL for patients ≥ 17 years of age and Haemo-QoL for patients 12 to < 17 years of age, HAL (≥ 17 y) and pedHAL (12 to < 17 y), PGIC-H, and EQ-5D-5L. Considering the open-label design, the relevance of PRO data is limited.

One of the exploratory endpoints includes data on the total coagulation factor product consumption and coagulation factor product consumption unrelated to bleeding events was provided upon request.

Importantly, definitions of bleeding events were pre-specified in the study protocol, are clearly stated and in line with ISTH guidelines.

Statistical methods

Based on the mITT population (including all patients who completed OP and received at least 1 dose of PF-06741086 in ATP, excluding patients that received inhibitors) non-inferiority of PF-06741086 was estimated using a repeated measure negative binomial regression model, which is considered appropriate. The derivation of the Non-inferiority (NI) margin of 2.5 for the primary efficacy endpoint can be followed statistically.

Three supplementary analyses were conducted to assess the impact of preventative treatment for medical/dental procedures, sport activity or physical therapy (plus 72 hours) (1), of PF-06741086 dose increase (2), and of treatment discontinuation (3). Additionally, three sensitivity analyses were conducted to assess the impact of carry-over effect from OP to ATP (1), the seasonal effect on bleeding (2) and the potential impact of excluded patients from mITT due to not successfully complete the OP and/or not meeting the eligibility criteria to enter ATP (3). The approaches used for each supplementary analysis and sensitivity analyses appear generally appropriate. The start date of the matched ATP period to assess seasonal effect is calculated as start date of OP +365; and the end date of the matched ATP period is calculated as end date of OP +365 or the discontinuation date during ATP, whichever is earlier.

The planned subgroup analyses, the sample size determination, and the adjustment for multiplicity do not raise concerns.

Efficacy data and additional analyses

Results

Baseline demographics

Of the 128 non-inhibitor participants in study B7841005, 101 had haemophilia A and 27 had haemophilia B. 20 of these participants were adolescents (2 on-demand during OP, 18 prophylaxis at OP), 15 of which had haemophilia A, 5 had haemophilia B (all with prophylaxis during OP), based on the all safety set.

The number of haemophilia B participants is considered low, especially since very limited previous clinical experience with marstacimab, which constitutes a first in class, is available.

While it is considered acceptable to include both HA and HB patients into the study, a sufficiently large number of subjects for each haemophilia type is necessary to enable a meaningful extrapolation to the general patient population. This was emphasised during EMA scientific advice, where the applicant was advised to "enrol a sufficiently large number of subjects in each stratum to achieve a treatment effect estimate with reasonable precision for both haemophilia A and B patients [...]" . It is noted that numbers provided for haemophilia B patients are also very limited compared to other clinical programmes, including those for factor replacement therapy for which substantially more clinical experience is available. Further, numbers for adolescents with HB are very low. This issue was initially raised as an MO, but could be resolved after additional data from LTE study 1007 were provided (further discussed below).

A severe bleeding phenotype was characteristic of the study population. In the on-demand modified intent-to-treat (mITT) population at the study entry all participants had one or more target joints and 36% had 3 or more target joints, while in the routine prophylaxis cohort 56.6% of the participants had one or more target

joints at study entry and 15.7% had 3 or more target joints at study entry despite being compliant with prophylactic factor replacement therapy.

In line with inclusion criteria, the minimum weight reported from participants of the pivotal phase 3 study B7841005 was 35.0 kg. No data were available for patients below this weight threshold, and benefit/risk could consequently not be concluded for patients with a body weight <35 kg. A respective MO could be resolved after the Applicant agreed to amend the indication and included the body weight threshold of 35 kg used in the clinical development programme.

In EMA protocol assistance (EMEA/H/SA/3363/2/2017/PA/II), the applicant was advised to obtain data from elderly and very elderly patients and the age restriction of adults was consequently increased from <65 years of age to <75 years of age. However, data from only 1 patient above 65 years of age were available.

Primary endpoint

The primary analysis demonstrated non-inferiority of marstacimab prophylaxis compared to routine prophylaxis at OP. The mean ABR of treated bleeds in the non-inhibitor cohort was 5.08 (95% CI: 3.40, 6.77) during the active treatment period compared to 7.85 (95% CI: 5.09, 10.61) during the observational period with routine prophylaxis, with a resulting estimated ABR difference of -2.77 (95% CI: -5.37, -0.16). Since non-inferiority was demonstrated, pre-specified statistical testing for superiority was performed and demonstrated superiority with a 2-sided p-value of 0.0376.

A reduction of the percentage of participants with 0, 1, or 2 bleeds was noted, while the percentage of participants with ≥ 3 bleeds was slightly increased (36.1% during routine prophylaxis, 39.8% during marstacimab prophylaxis).

The ABR for treated bleeds reported for patients in the routine prophylaxis OP seemed comparably high, and an OC was raised in this regard in the D120 LoQ. In the responses, the applicant identified a subpopulation of 15 patients on routine prophylaxis whose prophylaxis schedule adherence was <80%. For these patients, the model-derived ABR during OP was 21.54 (95% CI: 11.05, 32.03), and 6.63 (95% CI: 2.59, 10.68) during marstacimab ATP. After exclusion of the poor-adherence participants, an overall model-derived ABR of 4.73 (95% CI: 2.89, 6.58) during ATP was reported compared to 4.83 (95% CI: 3.07, 6.59) during the OP. From the provided data, it seems likely that this patient subset was the root cause for a comparably high ABR in the routine prophylaxis observational period of study B7841005.

For patients previously on on-demand treatment during OP, marstacimab prophylaxis demonstrated superiority with a 2-sided p-value of <0.0001, providing support for the prophylaxis OP cohort, which is considered to be of higher regulatory importance. The mean estimated ABR was 3.18 (95% CI: 2.09, 4.85) for marstacimab prophylaxis compared to 38.00 (95% CI: 31.03, 46.54) for on-demand treatment, with an estimated ABR ratio of 0.084 (95% CI: 0.059, 0.119). The percent reduction in the ABR of treated bleeds from the OP was 91.6%. As the upper bound of the 95% CI for the ABR ratio was less than 0.5, these results achieved the predetermined criterion for establishing the superiority with a 2-sided p-value of <0.0001. However, it is of note that in haemophilia patients without inhibitors, on-demand prophylaxis data can only be considered supportive as it does not reflect the standard of care in many EU countries.

Subgroup analyses for the primary analysis

Subgroup analyses for type of haemophilia, age groups, race, ethnicity, and geographic region were conducted:

The ABR for participants with haemophilia A was 5.30 for marstacimab prophylaxis compared to 9.16 for routine prophylaxis during OP.

The ABR for participants with haemophilia B was 4.71 for marstacimab prophylaxis compared to 3.26 for routine prophylaxis during OP.

The ABR for adult participants was 5.73 for marstacimab prophylaxis compared to 9.06 for routine prophylaxis.

The ABR for adolescent participants was 2.98 for marstacimab prophylaxis compared to 3.30 for routine prophylaxis during OP. Within the subpopulation of adolescent patients, HA adolescents had an ABR of 1.55 for marstacimab prophylaxis compared to 3.56 for routine prophylaxis. HB adolescents had an ABR of 7.62 for marstacimab prophylaxis compared to 2.45 for routine prophylaxis. This result for HB adolescents is derived from the results of only 4 patients. Two of which had 0 treated bleeding events during marstacimab ATP, and two had a substantial increase in treated bleeding events compared to the OP. One patient had 3 treated bleeds during OP and 16 treated bleeds during marstacimab prophylaxis, the majority of which were traumatic bleeds. Another subject had 0 treated bleeds at OP and 11 treated bleeds with marstacimab prophylaxis, all of which protocolled as traumatic in nature. Given the small sample of adolescent HB patients, results in this patient population are difficult to interpret.

The overall number of HB patients included into clinical trials across the clinical investigation programme for marstacimab was very low (n=28). Subgroup analyses in pivotal phase 3 study B7841005 showed that marstacimab prophylaxis trended worse compared to routine prophylaxis during the observation period, with corresponding ABRs of 4.71 and 3.26, respectively. HB patients were also markedly overrepresented in the patient subgroup who required dose escalation (HB: 8/25, 32.0%, HA: 6/91, 6.6%). In the very limited HB adolescent subpopulation (n=4), ambiguous efficacy results were reported. The safety database for haemophilia B, even taking into account the rarity of the disease, was also extremely limited. These factors resulted in uncertainties during the evaluation regarding efficacy and safety in the HB population, which could be resolved after additional data from the LTE study 1007 became available for review. In detail, the comparably worse ABR trend in HB patients was not substantiated in the LTE study 1007, where a lower ABR was reported. The mean estimated ABR in the overall HB population was 2.1 (95% CI: 0.96-4.58), thereof a mean ABR 1.77 (95% CI: 0.45-6.93; n=7) was reported for patients who were previously treated with on-demand factor treatment, and a mean ABR of 2.24 (95% CI: 0.88-5.74, n=17) for those previously on routine prophylaxis. Comparably higher ABR reported from the small HB patient sample (n=18) with previous routine prophylaxis was primarily caused by 2 patients with high individual annualised bleeding rates. Both patients showed ABR decreases in LTE study 1007 after dose escalation. Additionally provided data reported a trend for overall continually decreasing ABR values when analysed according to 6-month intervals.

While the proportion of HB participants who received dose escalation was higher in the HB patient population (32.0%) compared to HA (6.6%), the difference in patients who reached eligibility criteria for dose escalation was less pronounced between disease types. From newly provided data, overall 38.4% (35/91) of HA participants met dose escalation criteria compared to 48% (12/25) of HB participants. Since dose escalation was not mandatory and the decision to escalate a participant's dose was at the discretion of the investigator, an element of personal preference of the investigator might have impacted the reported proportion of dose escalated patients. In line with this argument, a large proportion of dose escalated HB patients were from one site.

Regarding the very limited sample of HB adolescents, all 4 patients rolled over into LTE 1007. 2 patients had ABRs of 0 during marstacimab ATP in the pivotal study 1005, and both patients maintained ABRs of 0 during

the LTE study 1007 without dose escalation. For both other patients, increased physical activity was noted during ATP, with a high frequency of traumatic bleeds in both patients, and both patients had lower ABRs during the LTE. The provided new information partly alleviated the concerns raised regarding efficacy in the HB adolescent study population.

Dose escalation to 300 mg QW resulted in a reduction in the mean ABR for participants during the ATP in both the prophylaxis (descriptive mean ABR (Q1, Q3) before dose escalation 14.03 (7.69, 19.48) and 3.42 (0.00, 4.68) after) and the on-demand groups (descriptive mean ABR (Q1, Q3) before dose escalation 3.57 (1.19, 8.03) and 2.98 (0.00, 6.89) after).

From efficacy listings of patients on marstacimab prophylaxis, several non-responders or poor-responders were identified. Upon request, the Applicant identified potential prognostic factors for poor responders to be adult age group, a higher percentage of overall haemophilic arthropathy as well as a higher HJHS total score. However, the analysis was not considered sufficiently robust for the potential prognostic factors to be reflected in the SmPC.

For patients previously treated with on-demand regimen during OP, improvement with marstacimab prophylaxis was evident across all subgroups analysed. Notably, HB patients previously on on-demand therapy responded well to marstacimab prophylaxis, which decreased the ABR of treated bleeds from overall 28.67 to 1.65. Also, the two adolescent HA patients in the on-demand cohort showed improved control of bleeding with marstacimab prophylaxis, with the combined ABR decreasing from 35.12 during on-demand OP to 1.52 during marstacimab treatment.

Sensitivity analyses for the primary endpoint

Sensitivity analyses were prospectively defined to investigate the impact of preventative infusions, marstacimab dose escalation (by including data after dose escalation into the analysis), treatment discontinuation, carryover effect from OP to ATP (by excluding data from the first month of marstacimab treatment), and seasonal effects (by including only the portion of ATP into the analysis that match the calendar time of the OP).

Prophylaxis at OP cohort

The estimate for the treatment effect difference between routine prophylaxis and marstacimab prophylaxis was -2.77. Analysis with inclusion of bleedings during preventative infusions increased the treatment estimate difference to -2.82. As prespecified in the SAP, for the primary endpoint data collected after optional dose escalation were not included into the analysis. The sensitivity analysis with inclusion of data after dose escalation showed an increase in treatment estimate difference to -3.20. Imputing the portion after dose escalation using data from before the dose increase led to a comparable delta of -2.74. Sensitivity analysis investigating the impact of treatment discontinuations was performed via imputing the portion after discontinuation using data from during the treatment and led to an increased delta of -3.12. Impact of carryover from OP to ATP was investigated by excluding data from the first month after initiation of marstacimab treatment. This analysis led to a decrease in treatment effect differences to -2.56. Seasonal effects were investigated by inclusion of only the portion of ATP matching the calendar time of OP, which showed an increase in delta to -4.40 (95% CI: -7.10, -1.70; 2-sided p-value=0.0014). The mean duration of matched ATP was only marginally lower than the duration of OP due to a low discontinuation rate. Across all participants in the mITT Analysis Set, 3.4% (4/116) did not have a matched ATP period due to early withdrawal.

ABRs were lower during the second 6 months of marstacimab compared to the first 6 months, with mean ABR estimates of 3.54 for the first half of ATP and 2.82 for the second half of ATP, when excluding subjects who required a dose increase.

Summaries provided based on ABR values at OP (groups: ABRs of 0 to <5, 5 to <10, 10 to <20, or ≥20) were provided with responses. In line with post-hoc sensitivity analyses of the primary analysis, for all secondary bleeding endpoints an increase in mean ABR was reported from the patient group with the lowest ABRs (0 to <5 at OP). Joint bleeds: 0.94 (SD 1.465) vs 2.88 (SD 4.866), spontaneous bleeds: 0.89 (SD 1.419) vs 2.61 (SD 5.130), target joint bleeds: 0.29 (SD 0.925) vs 1.66 (SD 4.675), total bleeds: 1.41 (SD 1.727) vs 4.29 (6.937). For all remaining groups, a mean decrease in ABR was reported under marstacimab treatment.

Taken together, the provided sensitivity analyses supported the obtained results from the primary analysis in non-inhibitor patients previously on routine prophylaxis. While some carryover from OP to ATP might have occurred, the corresponding sensitivity analysis showed a robust treatment effect difference of -2.56. All other sensitivity analyses led to an increase in delta, strengthening the obtained result of the primary endpoint. The treatment effect was stable over the course of one year of active treatment with marstacimab prophylaxis, with lower ABR values in the second half of treatment for those subjects who did not require a dose escalation.

On-demand cohort

The same set of sensitivity analyses as for patients previously on routine prophylaxis during OP were conducted for the patient cohort with on-demand treatment during OP.

The ratio estimate for the treatment effect comparison of on-demand treatment/marstacimab prophylaxis was 0.084. Sensitivity analyses regarding preventative infusions, impact of dose escalation, treatment discontinuations, and impact of carryover showed a comparable result as for the primary analysis (ratios between 0.082 and 0.084). The analysis to assess the seasonal effect on bleeding via inclusion of only the portion of ATP matching the calendar time of OP showed a notable reduction of the treatment effect ratio in favour of marstacimab to 0.062 (95% CI: 0.043, 0.090; 2-sided p-value<0.0001). A comparison of the first and second half of the marstacimab active treatment period reported a decrease in ABR during the second six months, in line with results obtained from the cohort of patients previously on routine prophylaxis. The treated ABR during the matched ATP period was numerically lower than the ABR during the overall ATP period in both cohorts. These supplementary data support the primary analysis with no concerns raised.

Secondary endpoints

Secondary endpoints evaluated incidences of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds. For all these bleeding related endpoints, in patients previously on routine prophylaxis a reduction of the overall incidence was demonstrated and results of the bleeding related secondary endpoints provide support for the primary analysis. However, a reduction in 0 bleeders is noted across all bleeding related secondary endpoints. Results for patients previously on routine prophylaxis are summarised below.

The incidence of joint bleeds was 4.13 during marstacimab ATP and 5.66 during previous routine prophylaxis. Annualised rates of participants with 0, 1 or 2 joint bleeds decreased (0 joint bleeds: 40/83 [48.2%] during routine prophylaxis to 33/83 [39.8%]), rates of participants with ≥3 joint bleeds increased from 23/83 (27.7%) to 27 (32.5%). The incidence of joint bleeds was lower in the second half of the ATP (3.07 vs 2.30).

The incidence of spontaneous bleeds was 3.78 during marstacimab ATP and 5.86 during previous routine prophylaxis. Annualised rates of participants with 0 spontaneous bleeds decreased slightly from 40/83 (48.2%) during routine prophylaxis to 35/83 (42.2%) during marstacimab prophylaxis, rates of participants with 1, 2, 3 or more spontaneous bleeds were comparable between treatment courses. The incidence of spontaneous bleeds was lower in the second half of the ATP (2.80 vs 2.03).

The incidence of treated target joint bleeds was 2.51 (95% CI: 1.25, 3.76) during marstacimab ATP and 3.36 (95% CI: 1.59, 5.14) during previous routine prophylaxis. Annualised rates of participants with 0 treated target joint bleeds decreased from 62/83 (74.7%) during routine prophylaxis to 54/83 (65.1%), rates of participants with 1, 2, 3 or more treated target joint bleeds were comparable between marstacimab and previous routine prophylaxis. The incidence of treated target joint bleeds was lower in the second half of the ATP (1.46 vs 1.29).

The incidence of total bleeds was 5.97 (95% CI: 4.13, 7.81) during marstacimab ATP and 8.84 (95% CI: 5.97, 11.72) during previous routine prophylaxis. Annualised rates of participants with 0 total bleeds decreased from 28/83 (33.7%) to 22/83 (26.5%), rates for those with 3 or more total bleeds increased from 33/83 (39.8%) to 39/83 (47.0%). The incidence of total bleedings was lower in the second half of the ATP (3.54 vs 1.29).

The key secondary endpoint percentage of participants with 0 bleeds was removed more than 2 years after study initiation as part of protocol amendment 7. At the time of endpoint removal, 127/128 patients were enrolled in study B7841005, of which 104 patients had already received Hympavzi. Taking into account the unfavourable outcome reported for marstacimab and the open-label design of pivotal study B7841005, it seems likely that the decision to remove the endpoint was data-driven. This is seen critical and raises uncertainties regarding study conduct. Since corresponding data on the percentage of participants with no treated bleeds were presented as part of the descriptive summary of the primary endpoint, this issue was however not further pursued.

It is noted that during the marstacimab ATP 5 participants discontinued. All 5 participants were included in the primary and subgroup analyses until discontinuation. 4/5 patients discontinued due to withdrawal by subject, 1 due to an AE (meningioma, unrelated to study drug). Only 2 of the 5 discontinued participants had higher ABRs (treated, joint, spontaneous, target, and total bleeds) during marstacimab treatment.

The haemophilia joint health score (HJHS) demonstrated comparable results for previous routine prophylaxis and marstacimab prophylaxis. Results after 12 months trended slightly better compared to results after 6 months, in line with the primary analysis and bleeding related secondary endpoints.

PROs

Overall, results from PROs suggested preservation of the benefits of routine prophylaxis under continued marstacimab treatment. However, due to the open-label design and the consequent considerable risk for bias, the relevance of PRO data is considered limited.

Development of antibodies

No relevant difference in ABRs was detected between patients with or without ADAs or nABs.

Supportive studies

The Phase 3 OLE Study B7841007, long-term OLE of the pivotal Study B7841005, is still ongoing and, according to the currently available data, in participants with varying lengths of treatment (34.0 to 483.0 days) marstacimab maintained its long-term efficacy with respect to ABR of treated bleeds and the incidence

of spontaneous bleeds, joint bleeds, total bleeds (treated and untreated), target joints, and HRQoL outcomes. Feasibility of self-administration using the sponsor's PFP device was established in a small patient population.

The multiple ascending dose study B7841002 showed that marstacimab efficacy across all doses investigated overall as well as across individual treatment groups. However, no clear dose/effect correlation could be deduced from the data provided given the small sample size.

The phase 2 OLE study B7841003 provided efficacy data in line with the results obtained in phase 3 studies.

2.6.7. Conclusions on the clinical efficacy

Non-inferiority and statistical superiority regarding the ABR of treated bleeds were shown for weekly marstacimab prophylaxis over a prospectively conducted lead-in observational period on routine factor prophylaxis in the overall study population. Generally, this outcome was supported by secondary endpoints regarding bleeding incidences and haemophilic joint assessment.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Study B7841005 – Pivotal Study

As of 17 April 2023, the LPLV for the non-inhibitor cohort:

- 37 participants with prior on-demand treatment using factor replacement entered the study, of whom 34 (91.9%) completed the 6-month OP and 3 (8.1%) discontinued during the OP (2 participants due to protocol deviations and 1 participant due to other reason of moving to a different country). Of the 34 participants who completed the OP, 33 participants entered the ATP and all 33 (100%) participants completed the 12 month ATP. No participants discontinued during the ATP.
- 91 participants with prior prophylactic treatment using factor replacement entered the study, of whom 84 (92.3%) completed the 6-month OP and 7 (7.7%) discontinued during the OP (5 participants no longer met eligibility criteria and 2 participants due to protocol deviations). Of the 84 participants who completed the OP, 83 participants entered the ATP, of whom 78 (94.0%) completed the 12-month ATP and 5 (6.0%) discontinued (4 participants withdrew and 1 participant due to AE).
- 108 of 111 participants who completed the 12-month marstacimab ATP planned to participate in the long-term extension Study B7841007.
- 1 participant with prior on-demand treatment and 8 participants with prior prophylactic treatment entered the follow-up phase of Study B7841005. Note: participants who planned to participate in the long-term extension Study B7841007 were not required to enter the follow-up phase.
- Two participants (1 in the prior on-demand cohort and 1 in the prior prophylaxis cohort) completed the OP, but discontinued before entering the ATP and marstacimab dosing due to not meeting eligibility criteria to enter the ATP.

Integrated Safety Analysis Population

In the integrated analyses datasets:

- Of 116 participants without inhibitors who entered the ATP phase of the Study B7841005, 111 (95.7%) participants without inhibitors completed the 12-month marstacimab ATP. As of 10 February 2023, 90 participants completed Study B7841005 and, 88 of these entered Study B7841007 as of 10 March 2023. These 88 were included in the B7841005/B7841007 analysis (29/30 [96.7%] participants with prior on-demand treatment and 59/60 [98.3%] participants with prior prophylaxis). 2 participants without inhibitors did not continue into Study B7841007 due to sponsor decision (1 participant in on-demand treatment at OP cohort) and investigator decision (1 participant in routine prophylaxis at OP cohort).
- Of 27 participants who entered Study B7841002, 24 participants completed the study and 2 participants discontinued due to AEs and 1 participant withdrew from study. Of the participants who completed Study B7841002, 18 participants were enrolled into the OLE Study B7841003. 2 participants were newly enrolled into Study B7841003 at the 150 mg SC QW dose. Of these 20 participants, 18 (including the 2 participants enrolled de novo) completed Study B7841003 and 2 participants discontinued due to withdrawal by participant.

Table 47: Patient exposure Marstacimab Dataset (Data cut-off: Pivotal: April 17, 2023, OLE: March 10, 2023)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	-	-	-	-
Blinded studies (active -controlled)	-	-	-	--
Open studies	27 Phase 1 20 Phase 2 (18 from Ph1 + 2 new subjects) 116 Phase 3 -> 88 OLE	26 Phase 1 20 Phase 2 (18 from Ph1 + 2 new subjects) 116 Phase 3 -> 144 unique subjects	6 phase 1 10 phase 2 116 phase 3	125
Post marketing	-	-	-	-
Compassionate use	-	-	-	-

* Received at least 1 dose of active treatment

** ≥ 12 months continuous exposure data.

The Applicant has provided two different datasets for the safety evaluation.

The first is the safety analysis from the pivotal trial (B7841005), where a comparison for the same patients while receiving their usual haemophilia treatment during the OP (observational period) is possible.

The second encompasses all patients with haemophilia A or B without inhibitors who received marstacimab in multiple dose studies across the clinical trial programme. In addition, patients with inhibitors from the phase 1 and phase 2 studies are included in this dataset, but not patients with inhibitors from the respective cohort of the pivotal trial.

Data from 144 patients are available in those datasets, with 125 subjects exposed to treatment with marstacimab for a duration of 12 months or longer. 116 of those patients suffered from haemophilia A, while 28 subjects suffered from haemophilia B. Furthermore, 6 of the haemophilia A patients were displaying inhibitors and enrolled in an inhibitor cohort in a phase 1 or phase 2 study. Safety data from the inhibitor cohort of the pivotal study were not included in the integrated safety analysis.

The majority of subjects were between 18 and 44 years old, with a median age of 31.0 years. The number of subjects ≥ 65 years in the clinical trial programme is extremely limited. Only one patient, aged 66, was enrolled in the pivotal trial. The lower age limit for inclusion into the pivotal trial was 12 years, and data from 19 adolescents, 15 with HA and 4 with HB are available.

The majority of patients were White (50 %), followed by Asian (40.3%) and Black (9.0) subjects.

The cut-off date of the safety database was March/April 2023, and the Applicant was asked to submit an updated analysis of all events of death, SAE and AESI reported since, also for the cohorts of patients suffering from haemophilia A or B with inhibitors enrolled in the pivotal trial B7841005/ extension trial B7841007. With the responses to the D120 LoQ, the Applicant submitted a safety update with a new cut-off of 09 Oct 2023. As the participation of the non-inhibitor cohort in pivotal study 1005 was already complete with the original cut-off, additional data for the non-inhibitor cohort derive from long-term extension study 1007. In addition, supportive data from the inhibitor cohorts of studies 1005 and 1007 as well as paediatric study 1008 were made available.

2.6.8.2. Adverse events

Treatment-Emergent Adverse Events

Table 48: Incidence, CTCAE Grade of Treatment-Emergent Adverse Events (All Causalities) by System Organ Class and Preferred Term - Marstacimab Dataset

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						Missing or Unknown n (%)	Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)			
With any AE	73 (62.9)	22 (19.0)	7 (6.0)	0	0	0	0	80 (69.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (2.6)	0	0	0	0	0	0	3 (2.6)
Anaemia	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Iron deficiency anaemia	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Lymphadenopathy	1 (0.9)	0	0	0	0	0	0	1 (0.9)
CARDIAC DISORDERS	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Arrhythmia	1 (0.9)	0	0	0	0	0	0	1 (0.9)
EAR AND LABYRINTH DISORDERS	0	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.9)
Hypoacusis	0	1 (0.9)	0	0	0	0	0	1 (0.9)
Tympanic membrane perforation	0	0	1 (0.9)	0	0	0	0	1 (0.9)
EYE DISORDERS	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Eye pain	1 (0.9)	0	0	0	0	0	0	1 (0.9)
GASTROINTESTINAL DISORDERS	12 (10.3)	5 (4.3)	0	0	0	0	0	16 (13.8)
Dental caries	4 (3.4)	1 (0.9)	0	0	0	0	0	5 (4.3)
Diarrhoea	1 (0.9)	1 (0.9)	0	0	0	0	0	2 (1.7)
Dyspepsia	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Enteritis	0	1 (0.9)	0	0	0	0	0	1 (0.9)
Functional gastrointestinal disorder	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Gastritis	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Gastrooesophageal reflux disease	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Haemorrhoids	2 (1.7)	1 (0.9)	0	0	0	0	0	3 (2.6)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						Missing or Unknown n (%)	Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)			
Haemorrhoids thrombosed	1 (0.9)	1 (0.9)	0	0	0	0	0	1 (0.9)
Toothache	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Upper gastrointestinal haemorrhage	1 (0.9)	0	0	0	0	0	0	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	16 (13.8)	2 (1.7)	1 (0.9)	0	0	0	0	17 (14.7)
Chest pain	1 (0.9)	1 (0.9)	0	0	0	0	0	1 (0.9)
Fatigue	2 (1.7)	0	0	0	0	0	0	2 (1.7)
Injection site bruising	2 (1.7)	0	0	0	0	0	0	2 (1.7)
Injection site erythema	3 (2.6)	0	0	0	0	0	0	3 (2.6)
Injection site haematoma	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Injection site induration	2 (1.7)	0	0	0	0	0	0	2 (1.7)
Injection site oedema	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Injection site pain	1 (0.9)	1 (0.9)	0	0	0	0	0	2 (1.7)
Injection site pruritus	4 (3.4)	0	0	0	0	0	0	4 (3.4)
Injection site swelling	2 (1.7)	1 (0.9)	0	0	0	0	0	3 (2.6)
Ocular implant exposure	0	0	1 (0.9)	0	0	0	0	1 (0.9)
Peripheral swelling	2 (1.7)	0	0	0	0	0	0	2 (1.7)
Pyrexia	2 (1.7)	0	0	0	0	0	0	2 (1.7)
INFECTIONS AND INFESTATIONS	36 (31.0)	8 (6.9)	1 (0.9)	0	0	0	0	41 (35.3)
COVID-19	19 (16.4)	3 (2.6)	0	0	0	0	0	22 (19.0)
Conjunctivitis	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Ear infection	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Folliculitis	1 (0.9)	0	0	0	0	0	0	1 (0.9)
Herpes zoster	2 (1.7)	0	0	0	0	0	0	2 (1.7)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing or Unknown n (%)	Total n (%)
Influenza	2 (1.7)	0	0	0	0	0	2 (1.7)
Laryngitis	0	1 (0.9)	0	0	0	0	1 (0.9)
Nasopharyngitis	4 (3.4)	1 (0.9)	0	0	0	0	5 (4.3)
Otitis media	1 (0.9)	0	0	0	0	0	1 (0.9)
Otitis media chronic	0	1 (0.9)	0	0	0	0	1 (0.9)
Periodontitis	1 (0.9)	0	0	0	0	0	1 (0.9)
Pharyngitis	3 (2.6)	0	0	0	0	0	3 (2.6)
Pulpitis dental	1 (0.9)	0	0	0	0	0	1 (0.9)
Respiratory tract infection	1 (0.9)	0	0	0	0	0	1 (0.9)
Rhinitis	2 (1.7)	0	0	0	0	0	2 (1.7)
Tonsillitis	2 (1.7)	2 (1.7)	1 (0.9)	0	0	0	4 (3.4)
Upper respiratory tract infection	3 (2.6)	0	0	0	0	0	3 (2.6)
Urinary tract infection	1 (0.9)	0	0	0	0	0	1 (0.9)
Viral infection	1 (0.9)	0	0	0	0	0	1 (0.9)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	16 (13.8)	5 (4.3)	0	0	0	0	18 (15.5)
Animal bite	1 (0.9)	0	0	0	0	0	1 (0.9)
Contusion	7 (6.0)	1 (0.9)	0	0	0	0	7 (6.0)
Fall	3 (2.6)	0	0	0	0	0	3 (2.6)
Foot fracture	0	1 (0.9)	0	0	0	0	1 (0.9)
Head injury	2 (1.7)	0	0	0	0	0	2 (1.7)
Joint dislocation	1 (0.9)	0	0	0	0	0	1 (0.9)
Joint injury	2 (1.7)	0	0	0	0	0	2 (1.7)
Limb injury	1 (0.9)	0	0	0	0	0	1 (0.9)
Road traffic accident	1 (0.9)	0	0	0	0	0	1 (0.9)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing or Unknown n (%)	Total n (%)
Skin laceration	2 (1.7)	0	0	0	0	0	2 (1.7)
Snake bite	1 (0.9)	0	0	0	0	0	1 (0.9)
Testicular injury	1 (0.9)	0	0	0	0	0	1 (0.9)
Tooth fracture	1 (0.9)	2 (1.7)	0	0	0	0	2 (1.7)
Traumatic haemorrhage	0	1 (0.9)	0	0	0	0	1 (0.9)
INVESTIGATIONS	12 (10.3)	1 (0.9)	0	0	0	0	13 (11.2)
Activated partial thromboplastin time prolonged	1 (0.9)	0	0	0	0	0	1 (0.9)
Alanine aminotransferase increased	1 (0.9)	0	0	0	0	0	1 (0.9)
Aspartate aminotransferase increased	1 (0.9)	0	0	0	0	0	1 (0.9)
Blood cholesterol increased	1 (0.9)	0	0	0	0	0	1 (0.9)
Blood triglycerides increased	1 (0.9)	0	0	0	0	0	1 (0.9)
Fibrin D dimer increased	3 (2.6)	0	0	0	0	0	3 (2.6)
Gamma-glutamyltransferase increased	1 (0.9)	0	0	0	0	0	1 (0.9)
Glucose urine present	1 (0.9)	0	0	0	0	0	1 (0.9)
Haemoglobin decreased	1 (0.9)	0	0	0	0	0	1 (0.9)
Prothrombin fragment 1.2 increased	2 (1.7)	1 (0.9)	0	0	0	0	3 (2.6)
Red blood cell count increased	1 (0.9)	0	0	0	0	0	1 (0.9)
SARS-CoV-2 test positive	1 (0.9)	0	0	0	0	0	1 (0.9)
Weight increased	1 (0.9)	0	0	0	0	0	1 (0.9)
METABOLISM AND NUTRITION DISORDERS	2 (1.7)	0	1 (0.9)	0	0	0	3 (2.6)
Folate deficiency	1 (0.9)	0	0	0	0	0	1 (0.9)
Gout	0	0	1 (0.9)	0	0	0	1 (0.9)
Hyperlipidaemia	1 (0.9)	0	0	0	0	0	1 (0.9)
Vitamin B12 deficiency	1 (0.9)	0	0	0	0	0	1 (0.9)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing or Unknown n (%)	
Vitamin D deficiency	1 (0.9)	0	0	0	0	0	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	14 (12.1)	4 (3.4)	2 (1.7)	0	0	0	20 (17.2)
Arthralgia	3 (2.6)	1 (0.9)	0	0	0	0	4 (3.4)
Arthropathy	1 (0.9)	0	0	0	0	0	1 (0.9)
Back pain	2 (1.7)	0	0	0	0	0	2 (1.7)
Dupuytren's contracture	1 (0.9)	0	0	0	0	0	1 (0.9)
Haemarthrosis	0	1 (0.9)	1 (0.9)	0	0	0	2 (1.7)
Haemophilic arthropathy	1 (0.9)	0	0	0	0	0	1 (0.9)
Joint range of motion decreased	2 (1.7)	0	0	0	0	0	2 (1.7)
Muscle contracture	0	1 (0.9)	0	0	0	0	1 (0.9)
Muscle spasms	2 (1.7)	0	0	0	0	0	2 (1.7)
Neck pain	0	1 (0.9)	0	0	0	0	1 (0.9)
Pain in extremity	1 (0.9)	0	1 (0.9)	0	0	0	2 (1.7)
Synovitis	1 (0.9)	0	0	0	0	0	1 (0.9)
Tendonitis	1 (0.9)	0	0	0	0	0	1 (0.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	1 (0.9)	0	0	0	1 (0.9)
Meningioma	0	0	1 (0.9)	0	0	0	1 (0.9)
NERVOUS SYSTEM DISORDERS	10 (8.6)	2 (1.7)	1 (0.9)	0	0	0	13 (11.2)
Dizziness	1 (0.9)	0	0	0	0	0	1 (0.9)
Headache	6 (5.2)	1 (0.9)	1 (0.9)	0	0	0	8 (6.9)
Hypoesthesia	1 (0.9)	0	0	0	0	0	1 (0.9)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing or Unknown n (%)	
Migraine	2 (1.7)	0	0	0	0	0	2 (1.7)
Peripheral nerve lesion	0	1 (0.9)	0	0	0	0	1 (0.9)
PSYCHIATRIC DISORDERS	2 (1.7)	0	0	0	0	0	2 (1.7)
Anxiety	1 (0.9)	0	0	0	0	0	1 (0.9)
Depression	1 (0.9)	0	0	0	0	0	1 (0.9)
Nervousness	1 (0.9)	0	0	0	0	0	1 (0.9)
RENAL AND URINARY DISORDERS	0	0	1 (0.9)	0	0	0	1 (0.9)
Calculus urinary	0	0	1 (0.9)	0	0	0	1 (0.9)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.9)	0	0	0	0	0	1 (0.9)
Prostatitis	1 (0.9)	0	0	0	0	0	1 (0.9)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (5.2)	2 (1.7)	0	0	0	0	7 (6.0)
Cough	2 (1.7)	0	0	0	0	0	2 (1.7)
Epistaxis	0	1 (0.9)	0	0	0	0	1 (0.9)
Nasal congestion	1 (0.9)	0	0	0	0	0	1 (0.9)
Oropharyngeal pain	1 (0.9)	0	0	0	0	0	1 (0.9)
Respiratory disorder	1 (0.9)	0	0	0	0	0	1 (0.9)
Rhinitis allergic	2 (1.7)	1 (0.9)	0	0	0	0	3 (2.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	9 (7.8)	1 (0.9)	0	0	0	0	9 (7.8)
Acne	2 (1.7)	0	0	0	0	0	2 (1.7)

Number of Participants: by System Organ Class and Preferred Term	B7841005/B7841007 (N=116)						Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Missing or Unknown n (%)	
Eczema	1 (0.9)	0	0	0	0	0	1 (0.9)
Hand dermatitis	1 (0.9)	0	0	0	0	0	1 (0.9)
Pruritus	4 (3.4)	1 (0.9)	0	0	0	0	4 (3.4)
Rash	1 (0.9)	0	0	0	0	0	1 (0.9)
Skin mass	1 (0.9)	0	0	0	0	0	1 (0.9)
Xeroderma	1 (0.9)	0	0	0	0	0	1 (0.9)
VASCULAR DISORDERS		8 (6.9)	2 (1.7)	0	0	0	10 (8.6)
Haematoma		2 (1.7)	0	0	0	0	2 (1.7)
Haemorrhage		0	1 (0.9)	0	0	0	1 (0.9)
Hypertension		5 (4.3)	1 (0.9)	0	0	0	6 (5.2)
Hypotension		1 (0.9)	0	0	0	0	1 (0.9)
White coat hypertension		1 (0.9)	0	0	0	0	1 (0.9)

MedDRA v25.1 coding dictionary applied.

Table created by:/Volumes/app/cdars/prod/prjB784/nda1_cdisc/B784_SCS_BLA/saseng/cdisc3_0/macros/aesocptsev_t.sas

PFIZER CONFIDENTIAL Table Generation: 14JUN2023 (04:04)

Study B7841005(Data cutoff : 17APR2023;Database snapshot date : 05MAY2023); B7841007(Data cutoff : 10MAR2023;Database snapshot date : 14APR2023) Output File: ./nda1_cdisc/B784_SCS_BLA/t143131

Frequency of AEs for Participants with Dose Escalation

For Studies B7841005/B7841007, of the 18 participants who had a dose escalation from 150 mg QW marstacimab to 300 mg QW marstacimab:

- No participant experienced an SAE or an AE that led to discontinuation of study intervention.
- 8 (44.0%) participants experienced TEAEs (all causalities), the most frequently reported were arthralgia and COVID-19 infection (2 [11.1%] participants). Other TEAEs reported were joint range of motion decreased, injection site induration, laryngitis, rhinitis nasopharyngitis (each 1 [5.6%] participants). No other AEs in the ISR category were reported for Studies B7841005/B7841007. All TEAEs reported while participants received 300 mg marstacimab QW were mild or moderate in severity.
- 10 participants who had their dose escalated did not experience any TEAEs while they remained on the 300 mg QW dose.

For Studies B7841002/B7841003, of the participants whose treatment with marstacimab was initiated at 300 mg QW marstacimab and maintained on that dose :

- In Study B7841002, 11 (78.6%) participants treated with 300 mg SC QW dose of marstacimab reported TEAEs (31 events, 7 of which were considered treatment-related). 1 participant without inhibitors experienced a SAE (Grade 2 appendicitis, not related to treatment).
- In Studies B7841002/B7841003, there were 2 (14.3%) participants who reported injection site bruising, whilst injection site erythema, injection site haematoma, injection site haemorrhage, injection site induration, injection site pain, injection site pruritus, injection site reaction and injection site swelling were all reported in 1 of the 14 (7.1%) participants each.

Treatment-Related AEs

Study B7841005 collected “study treatment related AE” where study treatment is defined as marstacimab prophylaxis during the ATP. Therefore, there were no treatment-related TEAEs in the OP by design.

In the integrated analysis of the studies, treatment-related TEAEs across the integrated studies in the Marstacimab Dataset showed:

- In Study B7841005 during ATP which represents the initial 12 months of exposure, the most frequently reported treatment-related AEs were injection site pruritus and pruritus, each reported in 4 participants (3.4%), and prothrombin fragment 1.2 increased, and injection site erythema, each reported in 3 (2.6%) participants. All other treatment-related TEAEs were reported in <2% participants. All treatment-related TEAEs were of Grade 1 or 2 severity.
- In Study B7841007 which represents exposure of >12 to approximately 28 months, the most frequently reported treatment-related AEs were injection site bruising, injection site induration and injection site swelling, all reported in 1 (1.1%) participants. All treatment-related TEAEs were of Grade 1 or 2 severity. No other treatment-related TEAEs were reported.
- In Studies B7841005/B7841007 where unique participants were combined to present the entire marstacimab experience up to approximately 28 months at the intended dose, the most frequently reported treatment-related AEs were injection site pruritus and pruritus, each reported in 4 (3.4%) participants. All other treatment-related TEAEs were reported in <3% participants. All participants had treatment-related TEAEs of Grade 1 or 2 severity.
- In Study B7841002, where all participants received the intended or higher doses (150, 300, 450 mg) for 3 months, the most frequently treatment-related AEs were injection site pain and injection site swelling (each reported by 3 [11.5 %] participants). Other frequently reported ($\geq 5\%$) treatment-related AEs were injection site bruising, injection site induration, and hypertension (each reported by 2 [7.7 %] participants). Treatment-related TEAEs were of Grade 1 or 2 in severity for all participants with the exception of 4 (15.4%) participants who reported treatment-related Grade 3 events which included injection site pain, injection site swelling, blood fibrinogen decreased, pruritus and rash erythematous each reported in 1 [3.8%] participants).
- In Studies B7841002/B7841003 where unique participants were combined to present the entire marstacimab experience up to 15 months with doses at 150 or 300 mg for 12 months, the most frequently reported treatment-related AEs were injection site pain and injection site swelling (each reported in 3 participants [10.7 %]), injection site bruising, injection site induration, injection site reaction and hypertension were each reported in 2 (7.1 %) participants). For the majority (85.7%) of participants, treatment related TEAEs were of Grade 1 or 2 severity and Grade 3 reactions were only reported in 4 (14.3%) participants. These included injection site pain, injection site swelling, blood fibrinogen decreased, pruritus and rash erythematous each reported in 1 [3.6%] participants).

Table 47 provides an integrated overview of treatment-related TEAEs across relevant studies in the Marstacimab Dataset.

Table 49: Incidence of treatment-emergent adverse events by system organ class and preferred term (treatment related) – marstacimab dataset

Number (%) of Participants: by System Organ Class and Preferred Term	B7841002 (N=26) n (%)	B7841002/ B7841003 (N=28) n (%)	B7841005 (N=116) n (%)	B7841007 (N=87) n (%)	B7841005/ B7841007 (N=116) n (%)
With any AE	14 (53.8)	16 (57.1)	23 (19.8)	3 (3.4)	24 (20.7)
GASTROINTESTINAL DISORDERS	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Dyspepsia	1 (3.8)	1 (3.6)	0	0	0
Haemorrhoids	0	0	1 (0.9)	0	1 (0.9)
Haemorrhoids thrombosed	0	0	1 (0.9)	0	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (26.9)	10 (35.7)	13 (11.2)	3 (3.4)	15 (12.9)
Fatigue	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Injection site bruising	2 (7.7)	2 (7.1)	1 (0.9)	1 (1.1)	2 (1.7)
Injection site erythema	1 (3.8)	1 (3.6)	3 (2.6)	0	3 (2.6)
Injection site haematoma	0	1 (3.6)	1 (0.9)	0	1 (0.9)
Injection site haemorrhage	1 (3.8)	1 (3.6)	0	0	0
Injection site induration	2 (7.7)	2 (7.1)	1 (0.9)	1 (1.1)	2 (1.7)
Injection site oedema	0	0	1 (0.9)	0	1 (0.9)
Injection site pain	3 (11.5)	3 (10.7)	2 (1.7)	0	2 (1.7)
Injection site pruritus	1 (3.8)	1 (3.6)	4 (3.4)	0	4 (3.4)
Injection site reaction	0	2 (7.1)	0	0	0
Injection site swelling	3 (11.5)	3 (10.7)	2 (1.7)	1 (1.1)	3 (2.6)
Injection site warmth	1 (3.8)	1 (3.6)	0	0	0
Peripheral swelling	0	0	1 (0.9)	0	1 (0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Contusion	0	0	1 (0.9)	0	1 (0.9)
Occupational exposure to product	1 (3.8)	1 (3.6)	0	0	0
INVESTIGATIONS	5 (19.2)	5 (17.9)	3 (2.6)	0	3 (2.6)
Blood fibrinogen decreased	1 (3.8)	1 (3.6)	0	0	0
Fibrin D dimer increased	1 (3.8)	1 (3.6)	2 (1.7)	0	2 (1.7)
Prothrombin fragment 1.2 increased	0	0	3 (2.6)	0	3 (2.6)
Prothrombin time prolonged	1 (3.8)	1 (3.6)	0	0	0

Number (%) of Participants: by System Organ Class and Preferred Term	B7841002 (N=26) n (%)	B7841002/ B7841003 (N=28) n (%)	B7841005 (N=116) n (%)	B7841007 (N=87) n (%)	B7841005/ B7841007 (N=116) n (%)
Troponin I increased	1 (3.8)	1 (3.6)	0	0	0
Troponin increased	1 (3.8)	1 (3.6)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	1 (0.9)	0	1 (0.9)
Arthralgia	0	0	1 (0.9)	0	1 (0.9)
NERVOUS SYSTEM DISORDERS	0	0	1 (0.9)	0	1 (0.9)
Headache	0	0	1 (0.9)	0	1 (0.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (3.8)	1 (3.6)	4 (3.4)	0	4 (3.4)
Pruritus	1 (3.8)	1 (3.6)	4 (3.4)	0	4 (3.4)
Rash erythematous	1 (3.8)	1 (3.6)	0	0	0
VASCULAR DISORDERS	2 (7.7)	2 (7.1)	0	0	0
Hypertension	2 (7.7)	2 (7.1)	0	0	0

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 v25.1 coding dictionary applied.
 Table created by:/Volumes/app/cdars/prod/prjB784/ndal1_cdisc/B784_SCS_BLA/saseng/cdisc3_0/macros/aesocpt_t.sas
 PFIZER CONFIDENTIAL Table Generation: 01SEP2023 (04:07)
 Study B7841005(Data cutoff : 17APR2023;Database snapshot date : 05MAY2023); B7841007(Data cutoff : 10MAR2023;Database snapshot date : 14APR2023) Output File: ./ndal1_cdisc/B784_SCS_BLA/t143124
 Table 14.3.1.2.4 Marstacimab is for Pfizer internal use.

The highest reported CTCAE Grade of an adverse event in the complete dataset was 3 (of 5), with one such AE (tympanic membrane perforation) occurring in one adolescent subject. In study 1002/1003, six such AEs (one instance each of injection site pain, injection site swelling, blood fibrinogen decreased, pruritus generalised, rash erythematous, skull fracture, cerebral haemorrhage and arthralgia) were reported in 6 adult subjects. In studies 1005/1007, 8 such AEs, with one instance each of ocular implant exposure, tonsillitis, gout, hemarthrosis, pain in extremity, meningioma, headache and calculus urinary were reported in 6 adult subjects. Of these events, the injection site reactions, fibrinogen decreased, pruritus and rash were judged as treatment related by the Applicant, which is supported.

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 Applicant was asked to include all AEs regarded as treatment related as ADRs in section 4.8 of the SmPC or to justify their omission and has adequately justified the selection of AEs as ADRs, except for hypertension.

Hypertension SMQ was reported with more than twice frequency in the integrated dataset of Phase 2 studies 1002 and 1003 than in Phase 3 studies 1005/1007.

Table 50: Adverse events of special interest – marstacimab dataset

Number (%) of Participants by Event Type and Preferred Term	B7841002 (N=26) n (%)	B7841002/B7841003 (N=28) n (%)	B7841005 (N=116) n (%)	B7841007 (N=87) n (%)	B7841005/B7841007 (N=116) n (%)
HYPERTENSION (SMQ)	3 (11.5)	4 (14.3)	7 (6.0)	1 (1.1)	8 (6.9)
Hypertension	3 (11.5)	4 (14.3)	7 (6.0)	1 (1.1)	8 (6.9)

One participant from the PF-06741086 300 mg SC loading + 150 mg SC QW from study 1002 non-inhibitor dose cohort permanently discontinued from study due to a Grade 2 non-serious AE of hypertension, which was considered as treatment related by the investigator. At baseline, this patient had BP values within normal limits, and he experienced an AE of elevated BP at study day 58. The fact that on day 66 blood pressure values were still hypertensive despite last treatment being administered on day 58 cannot be considered proof of marstacimab not being causally related to this AE, as the steady state half-life of this monoclonal antibody is expected to be 16-18 days. Further, the AE of hypertension is reported as resolved at day 85, which aligns with the expected washout of marstacimab. Two further patients who experienced hypertension AEs in study 1002 did not have a medical history of hypertension.

According to the Vital signs chapter of Clinical Safety Summary, 7 patients in Study 1003 experienced SBP increase from baseline ≥ 30 mm Hg and/or supine DBP increase from baseline ≥ 20 mm Hg. Overall 10 patients experienced ≥ 30 mmHg elevation in their systolic BP, ≥ 20 mmHg elevation in their diastolic BP during the Phase 3 clinical studies 1005 and 1007, and as such, their proportion is remarkably lower compared to those found in the Phase 2 studies 1002 and 1003. Most of the elevations were episodic in nature, and they occurred in patients who were normotensive or even low-normotensive at the BL of Study 1005.

In the by-patient line listing, overall 15 patients from the 111 patients eligible to enter the extension study 1007 had permanent systolic BP elevations reaching the magnitude of 5-30 mmHg. There were two patients from this subpopulation with hypertension at baseline, but the remaining part of these patients were normotensive or even low-normotensive at the baseline of Study 1005.

Taking into account the narrative of one subject who discontinued from study B7841002 due to hypertension that resolved after stopping the study drug and the incidence of hypertension in 14% of subjects in phase 2 + extension studies and 7% of subjects in the phase 3 + extension studies, as well as the prolonged BP elevations occurring in normotensive patients during the Phase 3 studies it cannot be ruled out convincingly that hypertension is related to marstacimab treatment, even if taking into account the comorbidity of hypertension with haemophilia.

2.6.8.3. Serious adverse event/deaths/other significant events

AESI

Thromboembolic Events

Pivotal Trial

No participants reported thromboembolic events during the marstacimab ATP. For participants with prior on-demand treatment, no participants reported thromboembolic events during the OP or ATP.

For participants with prior routine prophylaxis, 1 (1.1%) participant reported a device occlusion (blocked port-a-cath) during the OP, which required hospitalization for the device to be successfully restored and the participant allowed to continue the study.

Integrated Safety Analysis Population

There were no thromboembolic events across Studies B7841002/B7841003 or Studies B7841005/B7841007 during marstacimab treatment.

One healthy participant in Study B7841009 (BE study) experienced a deep vein thrombosis and pulmonary embolism 9 days following a single dose of marstacimab (300 mg), and 29 days after vaccination with the AstraZeneca (ChAdOx1-S [recombinant] COVID-19 vaccine (second dose).

Thrombotic microangiopathy

Pivotal Trial

There were no reports of thrombotic microangiopathy in any participant in this study.

Integrated Safety Analysis Population

There were no reports of thrombotic microangiopathy events in any participant in any clinical study across the marstacimab program (including the OP of Study B7841005).

Disseminated intravascular coagulation/ consumption coagulopathy

Pivotal Trial

There were no reports of disseminated intravascular coagulation/consumption coagulopathy in any participant in this study.

Integrated Safety Analysis Population

There were no reports of disseminated intravascular coagulation/consumption coagulopathy in any participant in any clinical study across the marstacimab program (including the OP of Study B7841005).

Injection site reactions

Pivotal Trial

Per protocol, ISRs were only evaluated and reported during the ATP when marstacimab was administered, therefore, comparisons with rate on prior therapy are not feasible.

For participants with prior on-demand treatment, 2 (6.1%) participants reported an ISR event during the marstacimab ATP. Both ISRs were of Grade 1 severity.

For participants with prior routine prophylaxis, 9 (10.8%) participants reported an ISR event during the marstacimab ATP. All ISRs were of Grade 1 (8 [9.6%] participants) or Grade 2 (1 [1.2%] participant) severity.

1 participant experienced approximately 70 ISRs mostly reported as injection site pruritus, erythema, or induration, Grade 1 or 2. This participant tested positive for ADA (Study Days 60, 120, and 180) and positive for NAb (Study Day 120).

There were no discontinuations for the AE of ISR in either cohort.

Integrated Safety Analysis Population

In Study B7841005 during the ATP which represents the initial 12 months of exposure, 11 (9.5%) participants reported ISRs with the most frequently reported being injection site pruritus (4 [3.4%]) and erythema (3 [2.6%] participants). Most ISRs were mild (8.6%), with few moderate (0.9%) and no severe reactions.

In Study B7841007 which represents exposure of >12 to approximately 28 months, 3 (3.4%) participants reported ISRs. ISRs reported were injection site bruising, injection site induration and injection site swelling each in 1 participant [1.1%]. ISRs were mild (2.3%), or moderate (1.1%) with no severe reactions.

All participants in Study B7841005 who were administered marstacimab used the PFS exclusively. All participants transitioning into Study B7841007 were provided the PFP for marstacimab administration. All participants in Study B7841007 except 2 used the PFP exclusively. ISRs were reported with a lower frequency in Study B7841007 than in Study B7841005 which may reflect the method of administration.

In Studies B7841005/B7841007 where unique participants were combined to present the entire marstacimab experience up to approximately 28 months at the intended dose, 13 (11.2%) participants reported ISRs. Most ISRs were mild (10.3%), with few moderate (0.9%) with no severe reactions.

In Study B7841002, where all participants received the intended or higher doses (150, 300, 450 mg) for 3 months, 9 (34.6%) participants reported ISRs. Most injection site reactions were mild (23.1%), with few moderate (3.8%) or severe (7.7%) reactions. Injection site pain and injection site swelling (both Grade 3) were each reported in 1 participant in the 1.5 mL injection volume, 450 mg SC QW cohort. The participant with injection site pain was down titration to the 1 mL injection volume 300 mg SC QW. The increased frequency and severity of injection site reactions at the 450 mg dose level was considered to be related to the increased injection volume of 1.5 mL, delivered 3 times per dose (whereas the other cohorts received marstacimab injection volumes \leq 1 mL). These data indicate that the limits of tolerability were reached for some participants at this injection volume.

In Studies B7841002/B7841003 where unique participants were combined to present the entire marstacimab experience up to 15 months with doses at 150 or 300 mg, ISRs were reported in 10 (35.7%) participants. Most ISRs were mild (21.4%), with few moderate or severe (7.1%) reactions. Grade 3 events were as described in Study B7841002.

Severe hypersensitivity and anaphylactic reactions

Pivotal Trial

No severe or systemic cases of hypersensitivity or anaphylaxis occurred for participants with prior on-demand or routine prophylaxis during the OP or marstacimab ATP.

Integrated Safety Analysis Population

2 participants in Study B7841002 reported Grade 3 events in the anaphylactic reaction SMQ of pruritus and rash erythematous.

No other severe hypersensitivity events were observed in Studies B7841002, B7841003 or the non-inhibitor cohort of Studies B7841005/B7841007 including OP in B7841005. No hypersensitivity or anaphylactic reactions were reported in the 3 participants who also tested positive for ADA in Studies B7841002/B7841003 or in the 23 participants who tested positive for ADA in Studies B7841005/B7841007.

COVID-19 infections

Pivotal Trial

COVID-19 (SMQ) occurred in 19 (22.9%) prior routine prophylaxis participants during the ATP compared to 3 (3.3%) participants during the OP. Many participants entered the ATP as COVID-19 rates were rising in early 2022.

Marstacimab Dataset

No Covid-19 events occurred in subjects from clinical trial 1002/1003, 3 participants of trial 1007 reported Covid-19 events.

AEs Requiring Continuous Monitoring or Treatment Modification

Pivotal trial

Hypersensitivity and Cutaneous Adverse Reactions

No participants with prior on-demand treatment reported hypersensitivity cutaneous adverse reactions during the OP. However, 2 (6.1%) participants with prior on-demand treatment reported cutaneous reactions of pruritus, both mild or moderate in severity and considered related by the investigator, during the marstacimab ATP.

For participants with prior routine prophylaxis, 2 (2.2%) participants during the OP reported mild cases of cutaneous reactions of eczema and rhinitis allergic (1 [1.1%] each, not related), while 6 (7.2%) participants during the marstacimab ATP reported mild to moderate cases of cutaneous reactions of pruritus (2 [2.4%], related) and rhinitis allergic (2 [2.4%], not related), and conjunctivitis, eczema, and rash (1 [1.2%] each, not related).

Gastrointestinal Varices/Haemorrhoids

No participants with prior on-demand treatment reported gastrointestinal varices/haemorrhoids during the OP, while 1 (3.0%) participant with a history of hemorrhoids experienced a localised inflammatory Grade 2 (moderate) event of haemorrhoids thrombosed during the ATP. The participant's active dosing with marstacimab was not affected by this event.

No gastrointestinal varices/haemorrhoids events were reported for participants with prior routine prophylaxis during the OP or marstacimab ATP.

Integrated Safety Analysis Population

All reactions were observed in the pivotal trial and are described above.

Hypertension

Hypertension also qualifies as an AESI under the definition of AEs requiring continuous monitoring (eg, additional laboratory testing) or requiring treatment modification (eg, delay or discontinuation of study intervention). Hypertension was one of the most frequently reported AESI and is further discussed under the heading of treatment related AEs above.

In summary, adverse events were defined as AESIs if they were either related to the mode of action or the administration of marstacimab, which is endorsed.

No instances of thromboembolic events, thrombotic microangiopathy or DIC were reported in any patient suffering from haemophilia A or B without inhibitors across the clinical investigation programme. One TEE of deep vein thrombosis and pulmonary embolism was observed in a healthy volunteer in the bioequivalence study B7841009, which led to the early termination of this study.

The incidence of injection site reactions and hypersensitivity reactions was low across all clinical trials. Notably, one patient who was ADA positive and subsequently Nab positive, reported >70 ISR in the pivotal trial. The patient was nAb negative from study Day 183 and ADA negative from study Day 246. He did not report ISR from this time onward and rolled over into the OLE.

No special signals or risk emerge from the analysis of the AESIs for the intended label population.

SAE

Table 51: Summary of serious adverse events (all causalities) by system organ class and preferred term – marstacimab dataset

Number of Participants Evaluable for AEs	B7841002 (N=26)	B7841002/ B7841003 (N=28)	B7841005 (N=116)	B7841007 (N=87)	B7841005/ B7841007 (N=116)
Number(%) of Participants with Adverse Events: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Number of participants with Serious AE	4 (15.4)	7 (25.0)	7 (6.0)	2 (2.3)	9 (7.8)
EAR AND LABYRINTH DISORDERS	0	0	1 (0.9)	0	1 (0.9)
Tympanic membrane perforation	0	0	1 (0.9)	0	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	2 (7.1)	2 (1.7)	0	2 (1.7)
Chest pain	0	0	1 (0.9)	0	1 (0.9)
Inflammation	0	2 (7.1)	0	0	0
Peripheral swelling	0	0	1 (0.9)	0	1 (0.9)
HEPATOBILIARY DISORDERS	1 (3.8)	1 (3.6)	0	0	0
Cholelithiasis	1 (3.8)	1 (3.6)	0	0	0
INFECTIONS AND INFESTATIONS	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Appendicitis	1 (3.8)	1 (3.6)	0	0	0
Tonsillitis	0	0	1 (0.9)	0	1 (0.9)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	0	1 (0.9)	1 (1.1)	2 (1.7)
Contusion	0	0	0	1 (1.1)	1 (0.9)
Traumatic haemorrhage	0	0	1 (0.9)	0	1 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	0	1 (0.9)	1 (1.1)	2 (1.7)
Haemarthrosis	0	0	1 (0.9)	1 (1.1)	2 (1.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	1 (0.9)	0	1 (0.9)
Meningioma	0	0	1 (0.9)	0	1 (0.9)
NERVOUS SYSTEM DISORDERS	0	1 (3.6)	0	0	0
Generalised tonic-clonic seizure	0	1 (3.6)	0	0	0
Haemorrhage intracranial	0	1 (3.6)	0	0	0
SOCIAL CIRCUMSTANCES	1 (3.8)	1 (3.6)	0	0	0
Physical assault	1 (3.8)	1 (3.6)	0	0	0
VASCULAR DISORDERS	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Haemorrhage	1 (3.8)	1 (3.6)	1 (0.9)	0	1 (0.9)
Total preferred term events ^a	4 (15.4)	8 (28.6)	8 (6.9)	2 (2.3)	10 (8.6)

Number of Participants Evaluable for AEs	B7841002 (N=26)	B7841002/ B7841003 (N=28)	B7841005 (N=116)	B7841007 (N=87)	B7841005/ B7841007 (N=116)
Number(%) of Participants with Adverse Events: by System Organ Class and Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Total Number of Cases ^b	4 (15.4)	8 (28.6)	8 (6.9)	2 (2.3)	10 (8.6)
Total Number of Participants with Serious Adverse Events ^c	4 (15.4)	7 (25.0)	7 (6.0)	2 (2.3)	9 (7.8)
Total Number of Participants with Serious Adverse Events ^d	16				

A case is a single event or a series of related events not separated in time occurring in a single participant.
a. Total number of events per participant per cohort.
b. Number of cases that started in the cohort.
c. Total number of participants having an event that started in the cohort.
d. Overall count of participants that had a Serious adverse Event in any cohort.
Source of Serious AE is SDW(Safety Data Warehouse) or Argus.
For Study B7841003 SAEs reported for 2 participants occurred after their study participation, were not related to study drug by the PI, and were reported after the active collection period required by the protocol. Therefore, these SAEs were only recorded in the Safety database and not recorded in the Study database (AE record).
MedDRA v25.1 coding dictionary applied.

Only one SAE during the pivotal trial, peripheral swelling (right calf), was considered possibly related by the investigator. As it occurred in temporal relationship to initiation of treatment with marstacimab and no other alternative aetiology was identified, this assessment is endorsed. The leg swelling subsided spontaneously after 3 days without intervention, a thrombosis above knee was excluded by ultrasound diagnostic imaging. The other reported SAEs occurred during the OP, were bleeding in a target joint or had a different aetiology.

No other SAE was considered possibly or probably related to treatment, which can be followed from the provided narratives.

The two SAEs of inflammatory response to a spontaneous bleed were reported 30 and 60 days after the end of treatment with marstacimab in clinical trial 1003.

The SAE "peripheral swelling" was judged as related by investigator and sponsor and has provided background information on this event and a justification why it is not considered an ADR. The applicant explained that the swelling subsided without treatment and no VTE could be detected.

Deaths

No deaths were reported in any of the marstacimab studies up to the data cut-off (17 April 2023 for the pivotal study 1005, 10 March 2023 for its OLE 1007).

2.6.8.4. Laboratory findings

Generally, review of the change from baseline for blood chemistry and haematology/ other laboratory parameters showed no clinically important findings in laboratory values in Studies B7841002/B7841003 or the non-inhibitor cohort of Studies B7841005/B7841007.

Coagulation parameters were evaluated also as PD markers and are discussed in the clinical pharmacology section of this AR. Consistent with the mode of action of marstacimab, an unspecific activation of the coagulation system with increases of prothrombin fragment 1.2 and D-dimer could be shown.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

The Applicant has provided subgroup analyses with regard to type of haemophilia, age, race, ethnic background and region. No safety signals are observable in any of the investigated subgroups.

The indication of marstacimab is envisaged for patients 12 years or older, and data from a total of 19 subjects between 12 and <18 years of age are available for the safety evaluation in adolescents. The lowest weight in any participant in the pivotal trial was 35 kg.

Just one patient in the safety database was older than 65, thus the clinical experience in elderly subjects is extremely limited.

2.6.8.7. Immunological events

Testing ADA positive had no overall impact on the incidence or severity of SAEs, TEAEs, and AESIs. There was no notable pattern with regards to incidences of TEAEs reported for ADA-positive participants compared with ADA-negative participants. The TEAEs were all mild to moderate (Grade 1 or 2) for ADA-positive participants. No life-threatening events were reported.

In Study B7841002, the 3 participants who tested ADA positive for marstacimab had safety findings generally consistent with ADA-negative participants. None of the 3 participants tested NAb positive. All 3 participants continued into the long-term safety-follow-up Study B7841003, and tested ADA negative from baseline through the last study visit. No participant tested ADA positive in Study B7841003.

During pivotal Study B7841005, the 23 participants who tested ADA positive for marstacimab, including the 6 participants who tested NAb positive, had safety findings generally consistent with ADA-negative participants. 22 of the 23 ADA-positive participants tested ADA negative at the end of the study and 19 of the 23 ADA-positive participants continued into Study B7841007, as of the 10 March 2023 data cut-off. One of the 23 ADA positive participants in Study B7841005 tested ADA positive but NAb negative in Study B7841007.

In conclusion, the immunogenicity evaluation showed that most cases of ADA or NAb were low-titre and transient and did not impact the safety profile in a recognisable way.

2.6.8.8. 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 FVIII or FIX concentrates while being on marstacimab prophylaxis provide

reassuring evidence on the safety of treating breakthrough bleedings with lowest possible effective doses of FVIII or FIX preparations, as prescribed in the clinical study protocols.

TFPI is the natural inhibitor of tissue factor (TF), which is the most potent initiator of coagulation. Beyond its role in haemostasis, TF also has signalling activity and promotes pleiotropic inflammatory responses via protease-activated receptors. (Witkowsi *et al*, DOI: 10.1016/j.tcm.2015.12.001) In pathophysiological conditions with increased tissue factor expression, such as infection, sepsis, cancer and crush injuries, potentiation of the inflammatory response via concomitant TFPI inhibition could pose a risk of adverse reactions, especially thrombosis.

2.6.8.9. Discontinuation due to adverse events

Pivotal Trial

Study B7841005 compared AEs leading to discontinuation from study participation reported during the 6-month OP where participants continued their current factor replacement therapy in the form of on-demand or prophylactic treatment versus during the subsequent 12-month ATP where participants received marstacimab prophylaxis.

- No participants with prior on-demand treatment discontinued the study during the OP or ATP due to AEs.
- For participants with prior routine prophylaxis, no participants discontinued the study during the OP due to AEs and 1 (1.2%) participant discontinued the study during the ATP due to an SAE of meningioma not related to study intervention.

Integrated Safety Analysis Population

An integrated overview of discontinuations across relevant studies in Marstacimab Dataset showed:

- In Study B7841005 during the ATP, which represents the initial 12 months of exposure, 1 (0.9%) participant discontinued from study due to AEs (meningioma, not considered treatment-related).
- In Study B7841007 which represents exposure of >12 to approximately 28 months, no participants discontinued from study due to AEs.
- In Studies B7841005/B7841007 where unique participants were combined to present the entire marstacimab experience up to approximately 28 months at the intended dose, 1 (0.9%) participant discontinued from study due to AEs (meningioma, not considered treatment-related).
- In Study B7841002, where all participants received the intended or higher doses (150, 300, 450 mg for 3 months, 2 (7.7%) participants discontinued from study due to AEs (blood fibrinogen decreased and hypertension). These AEs were considered treatment-related.
- In Studies B7841002/B7841003 where unique participants were combined to present the entire marstacimab experience up to 15 months with doses at 150 or 300 mg for 12 months, 2 (7.1) participants discontinued from study due to AEs (blood fibrinogen decreased and hypertension). These AEs were considered treatment-related.

Only one subject discontinued from the pivotal trial due to an unrelated AE.

In general, study discontinuations and dose modifications were rare.

Two subjects discontinued a clinical study because of AEs blood fibrinogen decreased and hypertension, which were considered treatment related by the investigator and sponsor. The Applicant was asked to include these AEs into table 4.8 of the SmPC or to justify their exclusion. After reviewing the narrative for the event of "fibrinogen decreased", it is agreed with the sponsor that a relationship with marstacimab is unlikely. The AE of hypertension however, is considered to be an ADR.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Exposure

Data from 144 unique male patients are available in the safety database, with 125 subjects exposed to treatment with marstacimab for a duration of 12 months or longer. 116 of those patients suffered from severe haemophilia A, while 28 subjects suffered from severe haemophilia B. Furthermore, 6 of the haemophilia A patients were displaying inhibitors and enrolled in an inhibitor cohort in a phase 1 or phase 2 study. Safety data from the inhibitor cohort of the pivotal study were not included in the integrated safety analysis.

The majority of subjects were between 18 and 44 years old, with a median age of 31.0 years. The number of subjects ≥ 65 yo in the clinical trial programme is extremely limited. Only one patient, aged 66, was enrolled in the pivotal trial. The lower age limit for inclusion into the pivotal trial was 12 years, and data from 19 adolescents, 15 with HA and 4 with HB are available.

The majority of patients were White (50.0%), followed by Asian (40.3%) and Black (9.0%) subjects.

Pooling strategy

The Pooling strategy, where safety data from

- patients with or without inhibitors completing studies 1002 and 1003,
- patients without inhibitors on completing study 1005 and in the ongoing LTE study 1007

were included in the integrated safety analysis and the two prespecified pooled datasets (comparison dataset and Marstacimab dataset) were used in the integrated safety analysis, is considered to be adequate for the assessment of marstacimab safety in haemophilia A and B patients.

Adverse Events

The adverse event profile across the multiple dose trials 1002/1003 and 1005/1007 shows that 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 specific safety signal arises from the analysis of TEAEs.

In the integrated marstacimab dataset, the overall frequencies of AEs were noticeably higher in the Phase 2 studies (studies 1002 and 1003) compared to both the ATP of Study 1005 and in the combined marstacimab dataset of studies 1005/1007. Given the higher marstacimab doses in the dose finding study 1002 this disparity is not unexpected. Furthermore the frequencies of SAEs were also higher in the studies 1002 and 1003 when contrasted with the integrated marstacimab dataset in studies 1005/1007.

SAEs

From the overall SAE profile, no specific concerns arise.

Deaths

No deaths occurred during the clinical investigation programme until the data cut-off.

AESIs

The following AESIs were predefined and analysed: Thromboembolic events, thrombotic microangiopathy, disseminated intravascular coagulation/ consumption coagulopathy, injection site reactions, severe hypersensitivity and anaphylactic reactions, COVID-19 infections and other AEs requiring continuous monitoring or treatment modification including: haemorrhage, hepatic disorder, drug-induced liver injury, liver related investigations (transaminases, aspartate aminotransferase, and alanine aminotransferase), and hypertension.

TEEs/ thrombotic microangiopathy/ DIC/Consumption coagulopathy/ severe hypersensitivity and anaphylactic reactions

No such events were reported throughout the clinical development programme in subjects with haemophilia. One event of DVT/PE was reported in a healthy volunteer, concomitantly to a vaccination with Vaxzevria.

A specific warning on thromboembolic events has been added in section 4.4 of the SmPC. The use of other anti-tissue factor pathway inhibitor (anti-TFPI) products has been associated with the development of thromboembolic complications in patients exposed to additional haemostatic agents (i.e. bypassing agents) in close proximity. The benefit and risk of using Hympavzi in patients with a history of thromboembolic events or currently experiencing an acute severe illness should be considered. Patients at risk should be monitored for early signs of thrombosis, and prophylaxis 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 manage as clinically indicated. In addition, thromboembolism has been added as an important potential risk in the safety specification of the RMP and 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) will be initiated with the objective 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.

Injection site reactions

In Study B7841005, 11 (9.5%) participants reported ISRs with the most frequently reported being injection site pruritus (4 [3.4%]) and erythema (3 [2.6%] participants). Most ISRs were mild (8.6%), with few

moderate (0.9%) and no severe reactions. In Study B7841007, 3 (3.4%) participants reported ISRs. ISRs reported were injection site bruising, injection site induration and injection site swelling each in 1 participant [1.1%]. ISRs were mild (2.3%), or moderate (1.1%) with no severe reactions. All participants in Study B7841005 who were administered marstacimab used the PFS exclusively. All participants transitioning into Study B7841007 were provided the PFP for marstacimab administration. All participants in Study B7841007 except 2 used the PFP exclusively. ISRs were reported with a lower frequency in Study B7841007 than in Study B7841005 which may reflect the method of administration.

COVID-19 infections

COVID-19 (SMQ) occurred in 19 (22.9%) prior routine prophylaxis participants during the ATP compared to 3 (3.3%) participants during the OP. Many participants entered the ATP as COVID-19 rates were rising in early 2022. No Covid-19 events occurred in subjects from clinical trial 1002/1003, 3 participants of trial 1007 reported Covid-19 events.

Hypertension

Hypertension was one of the most frequently reported AESIs and was observed with an incidence of 14% of subjects in phase 2 + extension studies and 7% of subjects in the phase 3 + extension studies and has been included in the *table under section 4.8 of the SmPC*.

Discontinuation due to an AE

Only one subject discontinued from the pivotal trial due to an unrelated AE (meningioma). In general, study discontinuations and dose modifications were rare.

Special Populations

Subgroup analyses with regards to type of haemophilia, age, race, ethnic background and region were provided. No safety signals emerged in any of the investigated subgroups. The lower age limit is adequately reflected in sections 4.1 and 4.2 of the SmPC. The lower bodyweight limit is mentioned in section 4.2 and was included into section 4.1.

Laboratory evaluations

Generally, review of the change from baseline for blood chemistry and haematology/ other laboratory parameters showed no clinically important findings in laboratory values in studies B7841002/B7841003 or the non-inhibitor cohort of studies B7841005/B7841007. Coagulation parameters were evaluated also as PD markers and are discussed in the clinical pharmacology section of this AR. Consistent with the mode of action of marstacimab, an unspecific activation of the coagulation system with increases of prothrombin fragment 1.2 and D-dimer could be shown. Nonclinical data as well as clinical data from bleeding events treated with FVIII or FIX concentrates while being on marstacimab prophylaxis provide reassuring evidence on the safety of treating breakthrough bleedings with lowest possible effective doses of FVIII or FIX preparations, as prescribed in the clinical study protocols. This recommendation is also accurately reflected in sections 4.2 and 4.4 of the SmPC.

In pathophysiological conditions with increased tissue factor expression, such as infection, sepsis, cancer and crush injuries, potentiation of the inflammatory response via concomitant TFPI inhibition could pose a risk of adverse reactions, especially thrombosis. A statement pertaining to the management of patients with acute severe illness has been included in section 4.2 of the SmPC and a more detailed warning statement was added in section 4.4 of the SmPC to alert treating physicians to the potential risks of treatment with marstacimab during such disease states, especially with regards to thrombosis.

ADA

The immunogenicity evaluation showed that most cases of ADA or nAb were low-titre and transient and did not impact the safety profile in a recognisable way. In the pivotal study, 19.8% of subjects tested positive for ADA during the trial, with only 1 of 23 patients still ADA positive at the end of the study. All NAb were treatment induced and transient in nature. No participants were NAb positive at the end of the study.

Due to the small size of the safety database, only AEs with a frequency of up to "uncommon" can be detected. The cut-off date of the safety database was March/April 2023, and the Applicant was asked to submit an updated analysis of all events of death, SAE and AESI reported since, also for the cohorts of patients suffering from haemophilia A or B with inhibitors enrolled in the pivotal trial B7841005/ extension trial B7841007. A safety update with a new cut-off of 09 Oct 2023 was submitted. As the participation of the non-inhibitor cohort in pivotal study 1005 was already complete with the original cut-off, additional safety data for the non-inhibitor cohort derive from long-term extension study 1007. In addition, supportive data from the inhibitor cohorts of studies 1005 and 1007 as well as paediatric study 1008 were made available. These new data confirmed the observed safety profile of marstacimab and no new safety signals arose.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The available safety database for marstacimab as a prophylactic agent in haemophilia without inhibitors shows that injection site reactions and ADA development were the most frequently reported adverse events. No thromboembolic events or severe hypersensitivity or anaphylactic reactions were observed during the clinical trials.

A marketing authorisation for Hympavzi can be recommended from a clinical safety perspective.

The CHMP considers the following measures necessary to address issues related to safety:

- 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)

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 52: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Thromboembolism
Missing information	None

2.7.2. Pharmacovigilance plan

Table 53: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
A Post-Authorisation Safety Study to Evaluate the Safety of Marstacimab Among Patients with Severe Haemophilia A or B using Real-World Data in European Haemophilia Registers (B7841016) Planned	To evaluate the incidence rate of thromboembolic events among patients with severe haemophilia A or B in the patient cohort treated with marstacimab during routine clinical care, relative to comparator cohorts treated with standard of care, such as factor replacement therapy, and unexposed to marstacimab.	Thromboembolic events	Protocol submission	Within 6 months of approval for marstacimab
			Interim/Progress Reports	Interim Report: 4 years after the start of data collection Progress reports to be reported with PSURs after start of data collection.
			Final Report	Within 6 months after end of data collection, anticipated 30 June 2033.

2.7.3. Risk minimisation measures

Table 54: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Thromboembolism	<u>Routine risk communication:</u>

	<p><i>SmPC section 4.4</i></p> <p><i>PL section 2</i></p> <p><u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u></p> <p><i>None</i></p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p><i>None</i></p>
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2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Hympavzi (Marstacimab) is included in the additional monitoring list as it contains a new active substance which on 1st January 2011 was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

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

3.1.2. Available therapies and unmet medical need

The current standard of care for haemophilia A and B is replacement of the missing coagulation factor via exogenous factor VIII and IX products. Factor prophylaxis has to be administered via intravenous infusion up to 3 times weekly. Newer extended half-life products have reduced infusion frequency but still require IV access. For haemophilia A, Hemlibra is an option for prophylactic treatment by a subcutaneous route of administration. In addition, for the control of spontaneous or traumatic bleeding events, on demand infusion of FVIII or FIX products are frequently necessary despite baseline prophylaxis. Recently, gene therapy treatments have been approved for both haemophilia A (Roctavian) and Haemophilia B (Hemgenix) in patients without inhibitors against factors VIII or X respectively.

3.1.3. Main clinical studies

Study **B7841005** is an ongoing, one-way, cross-over, open-label, multi-centre study planned for approximately 145 adolescent and adult participants between 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 inhibitor, with approximately 20% of participants as adolescents (ages between 12 to <18 years old). The non-inhibitor cohort of this study is complete (N=111), whereas the inhibitor cohort is ongoing. The study duration for an individual participant is approximately 21 months, which includes a 45-day screening period, a 6-month observational phase (on-demand or routine prophylactic treatment), 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. Patients weighing at least 50 kg with 2 or more spontaneous (atraumatic) 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.

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 successfully completed the Phase 3 Study B7841005. 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. All participants are provided the pre-filled pen (PFP) for administration of marstacimab in the study. Feasibility of the PFP was evaluated in an optional open-label, single arm sub-study in 23 participants.

3.2. Favourable effects

The primary analysis demonstrated non-inferiority of marstacimab prophylaxis compared to routine prophylaxis at OP in a mixed population of HA and HB patients (combined analysis), as the ABR of treated bleeds in the non-inhibitor cohort was 5.08 (95% CI: 3.40, 6.77) during the active treatment period compared to 7.85 (95% CI: 5.09, 10.61) during the observational period with routine prophylaxis in the pivotal trial, with a resulting estimated ABR difference of -2.77 (95% CI: -5.37, -0.16). Since non-inferiority was demonstrated, pre-specified statistical testing for superiority was performed and demonstrated superiority with a 2-sided p-value of 0.0376. The ABR for participants with haemophilia A was 5.30 for marstacimab prophylaxis compared to 9.16 for routine prophylaxis during OP. The ABR for participants with haemophilia B was 4.71 for marstacimab prophylaxis compared to 3.26 for routine prophylaxis during OP.

In patients with insufficient response to 150mg weekly marstacimab, dose escalation to 300mg weekly marstacimab was effective in reducing mean ABR of treated bleeds (14.03 before dose increase, 3.42 after dose increase).

Robustness of results was investigated using supplemental and sensitivity analyses, including investigations of the impact of carryover, seasonal effects, dose escalation, and discontinuations, which strengthened the primary analysis.

The primary analysis was supported by secondary endpoints, which included investigations of the incidences of joint, spontaneous, target joint, and total bleeds. Non-inferiority was established for all bleeding rate secondary endpoints, with reductions in ABRs reported under marstacimab treatment compared to previous routine prophylaxis in all bleeding rate secondary endpoints.

For HA and HB patients without inhibitors previously on on-demand treatment during OP, marstacimab prophylaxis demonstrated superiority with a 2-sided p-value of <0.0001, providing support for the results of the prophylaxis OP cohort. The mean estimated ABR was 3.18 (95% CI: 2.09, 4.85) for marstacimab prophylaxis compared to 38.00 (95% CI: 31.03, 46.54) for on-demand treatment, with an estimated ABR ratio of 0.084 (95% CI: 0.059, 0.119). The number of participants with 0 treated bleeds increased from 1/33 (3.0%) during OP to 10/33 (30.3%) during ATP.

3.3. Uncertainties and limitations about favourable effects

Currently available data from HB patients is limited (N=28), with particular limitations of the HB adolescent population (N=4).

Among patients treated according to the dose escalation protocol, a marked overrepresentation of HB participants was noted. However, the proportion of patients eligible for dose escalation was largely comparable between haemophilia types, alleviating this uncertainty.

The ABR for treated bleeds reported for HA patients during routine prophylaxis OP was high compared to other clinical studies with routine prophylaxis factor VIII treatment arms, seemingly due to poor compliance of some participants at baseline.

Despite the decrease in ABRs across all bleeding rate related endpoints during marstacimab treatment, several marstacimab non-responders or poor-responders were identified.

Percentages of 0 bleeders were decreased compared to previous routine prophylaxis for all bleeding types (treated bleeds, joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds).

A small dose finding study (B7841002) was conducted but the results were inconclusive due to the low sample size for each treatment group.

3.4. Unfavourable effects

The adverse event profile across the multiple dose trials 1002/1003 and 1005/1007 shows that 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.

The immunogenicity evaluation showed that most cases of ADA or nAb were low-titre and transient and did not impact the safety profile in a recognisable way. In the pivotal study, 19.8% of subjects tested positive for ADA during the trial, with only 1 of 23 patients still ADA positive at the end of the study. All NAb were treatment induced and transient in nature. No participants were NAb positive at the end of the study.

No specific safety signal arises from the analysis of TEAEs, SAEs and AESIs.

No deaths occurred during the clinical development programme.

The cut-off date of the safety database was March/April 2023, and the Applicant was asked to submit an updated analysis of all events of death, SAE and AESI reported since, also for the cohorts of patients suffering from haemophilia A or B with inhibitors enrolled in the pivotal trial B7841005/ extension trial B7841007. The Applicant submitted a safety update with a new cut-off of 09 Oct 2023. As the participation of the non-inhibitor cohort in pivotal study 1005 was already complete with the original cut-off, additional data for the non-inhibitor cohort derive from long-term extension study 1007. In addition, supportive data from the inhibitor cohorts of studies 1005 and 1007 as well as paediatric study 1008 were made available. These new data confirmed the observed safety profile of marstacimab and no new safety signals arose.

3.5. Uncertainties and limitations about unfavourable effects

Due to the small size of the safety database, only AEs with a frequency of up to "uncommon" can be detected. Few patients with HB are included in the safety population, of whom only 4 were adolescents. Only one patient older than 65 was enrolled across all trials.

The use of other anti-tissue factor pathway inhibitor (anti-TFPI) products has been associated with the development of thromboembolic complications in patients exposed to additional haemostatic agents (i.e. bypassing agents) in close proximity. A specific warning on thromboembolic events has been added in section 4.4 of the SmPC. The benefit and risk of using Hympavzi in patients with a history of thromboembolic events or currently experiencing an acute severe illness should be considered. In addition, thromboembolism has been added as an important potential risk in the safety specification of the RMP and 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) will be initiated with the objective 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.

3.6. Effects Table

Table 55: Effects Table for Hympavzi as routine prophylaxis of bleeding episodes in patients 12 years of age and older with severe haemophilia A or B without inhibitors

Effect	Short Description	Unit	Treatment N=83	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ABR	pEP treated bleeds	Mean (95% CI)	5.08 (3.40, 6.77)	7.85 (5.09, 10.61) routine prophylaxis	- Several marstacimab non-responders or poor-responders were identified. - Percentages of 0 bleeders were decreased compared to previous routine prophylaxis for all bleeding types	Study B7841005
ABR HA population	Treated bleeds	Mean (SD)	5.30 (8.540)	9.16 (14.251) routine prophylaxis		Study B7841005
ABR HB population	Treated bleeds	Mean (SD)	4.71 (6.088)	3.26 (3.305) routine prophylaxis	Available data from HB patients is limited (N=28), with particular limitations of the HB adolescent population (N=4)	Study B7841005
Unfavourable Effects						
Injection site reactions	Including pain, swelling, bruising, pruritus, erythema	%	B7841005: 9.5 % B7841002/B7841003: 35.7 %	-	small size of the safety database(n=83)	Clinical safety section 2.6.8
Anti-drug antibodies		%	B7841005: 19.8 % B7841007: 2.3 %	-		Clinical safety section 2.6.8.
Neutralising antibodies		%	B7841005: 5.2 % B7841007: 0.0 %	-		Clinical safety section 2.6.8.

Abbreviations: ABR annualised bleeding rate

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Currently, the standard of care for patients with haemophilia A or B without inhibitors is replacement therapy with FVIII or FIX products, which necessitates treatment with regular intravenous infusions every 2 to 3 days. For newer extended half-life products, IV infusion intervals every week or even every 14 days can be sufficient, and for patients with haemophilia A, a subcutaneous prophylaxis option exists with Hemlibra. Hympavzi is administered via flat dose weekly subcutaneous injections (300mg initial loading followed by 150mg QW) for HA and HB patients ≥ 12 years of age above 35kg bodyweight). The proposed posology and method of administration are considered an important benefit, which are likely to increase treatment compliance, especially as venous access, which is often difficult to achieve, is not necessary.

The MAA for Hympavzi is mainly based on results from the single pivotal study B7841005 conducted in patients with severe HA or HB without inhibitors ≥ 12 years of age. Hympavzi effectively reduced the frequencies of bleeding events in the overall patient population when compared to routine FVIII or FIX replacement prophylaxis during a run-in period of at least 6 months in the same subjects. Non-inferiority and statistical superiority over routine prophylaxis were shown in the combined analysis. Further, superiority over on-demand treatment was established. These results were robust, as demonstrated with informative sensitivity analyses investigating impact of various potential sources of bias. In patients experiencing insufficient response to Hympavzi, dose escalation to 300 mg QW was effective in lowering the ABR of treated bleeds. The number of HB patients across the clinical programme was low (n=28), with particularly low numbers for adolescent HB patients (n=4), with ambiguous efficacy results reported from the pivotal study. However, updated efficacy data for HB patients from LTE study 1007 provided reassuring additional data, alleviating initially raised concerns regarding efficacy in HB patients.

With the currently available safety data, no specific safety signal arose from the analysis of TEAEs, SAEs, and AESIs, and the safety profiles of patients with HA and HB were comparable. Also, no specific safety signals were detected in the patient population who required a dose escalation. However, the size of the safety database is small, allowing only detection of adverse events up to the frequency rare. Updated safety data as well as supportive safety data for the inhibitor cohort of the pivotal trial and the ongoing paediatric trial confirmed the observed safety profile.

3.7.2. Balance of benefits and risks

Treatment response in HA and HB patients is considered sufficiently characterised.

While the number of HB patients across the clinical programme was low, with particularly low numbers of adolescents with HB, an update from the LTE study 1007 provided reassuring new data on the efficacy in HB patients, alleviating initially raised concerns regarding the treatment response in HB patients.

The observed safety profile is benign with comparable safety results in patients with HA and HB.

The wording in section 4.1 of the SmPC was amended versus originally proposed in order to account for the fact that no dose recommendation can be made for patients below 35 kg body weight since these patients were excluded from the trials.

Weighing the established effect of Hympavzi treatment in patients with HA and HB and taking into account remaining uncertainties due to a limited patient sample of HB patients against the overall benign safety profile reported from both HA and HB patients, the benefits of Hympavzi treatment are considered to exceed any risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Hympavzi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Hympavzi is not similar to Alprolix, Idelvion, Roctavian and Hemgenix within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Hympavzi is favourable in the following indications:

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

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that marstacimab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0443/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.