

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761369Orig1s000

INTEGRATED REVIEW

Integrated Review**Table 1. Application Information**

Application type	BLA
Application number(s)	761369
Priority or standard	Standard
Submit date(s)	10/11/2023
Received date(s)	10/11/2023
PDUFA goal date	10/11/2024
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	10/10/2024
Established/proper name	Marstacimab-hncq
(Proposed) proprietary name	HYMPAVZI
Pharmacologic class	Anti-tissue factor pathway inhibitor
Other product name(s)	PF-06741086
Applicant	Pfizer Inc.
Dosage form(s)/formulation(s)	INJECTION
Dosing regimen	The recommended dosing regimen comprise of a loading dose of 300 mg for the first week followed by once weekly dosing of 150 mg by subcutaneous injection. The recommended dosage of HYMPAVZI for patients 12 years of age and older, weighing at least 35 kg is as follows: • Day 1: Administer 300 mg (two 150 mg injections) by subcutaneous injection (loading dose) • Day 8 and thereafter: Administer 150 mg every week by subcutaneous injection
Applicant-proposed indication(s)/population(s)	For routine prophylaxis (to prevent or reduce the frequency of bleeding episodes) in adults and pediatric patients 12 years of age and older with: • Hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or • Hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
SNOMED CT code for proposed indication disease term(s)¹	234442002 (Hereditary factor VIII deficiency disease without inhibitor) 438792009 (Hereditary factor IX deficiency disease without inhibitor)
Regulatory action	Approval
Approved dosage (if applicable)	The recommended dosage of HYMPAVZI for adult and pediatric patients 12 years of age and older is as follows: <u>Loading dose</u> • 300 mg (two 150 mg subcutaneous injections) • If more than one injection is required to deliver a complete dose, administer each injection at a different injection site. <u>Maintenance dose</u> • One week after the loading dose, initiate maintenance dosing of 150 mg every week by subcutaneous injection on the same day each week, at any time of day.

BLA 761369

HYMPAVZI (marstacimab-hncq) injection

Approved indication(s)/ population(s) (if applicable)	For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: • hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or • hemophilia B (congenital factor IX deficiency) without factor IX inhibitors.
SNOMED CT code for approved indication disease term(s)¹	234442002 (Hereditary factor VIII deficiency disease without inhibitor) 438792009 (Hereditary factor IX deficiency disease without inhibitor)

¹ For internal tracking purposes only.

Abbreviations: DNH, Division of Nonmalignant Hematology; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ABR	annualized bleeding rate
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
ATP	active treatment phase
AUC	area under the concentration-time curve
BLA	biologics license application
CL	clearance
C _{max}	maximum plasma concentration
DDI	drug-drug interaction
DDIM	D-dimer concentration
dPT	diluted prothrombin time
EC ₅₀	half-maximal effective concentration
ECL	electrochemiluminescence
ECG	electrocardiogram
E-R	exposure-response
FDA	Food and Drug Administration
FIB	fibrinogen concentration
FMQ	FDA Medical Query
FIX	factor IX
FVIII	factor VIII
FX	factor X
GMR	geometric mean ratio
GCP	good clinical practice
HA	hemophilia A
Haem-A-QoL	Hematology A Quality of Life
HB	hemophilia B
IND	investigational new drug
IgG1	immunoglobulin G1
ISP	integrated safety population
IU	international units
IV	intravenous
M1	margin 1
M2	margin 2
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRHD	maximum recommended human dose
NAb	neutralizing antibody
NI	noninferiority
NOAEL	no observed adverse effect level

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OD	on-demand
OP	observational phase
OP-OD	observational phase on-demand
OP-PPX	observational phase prophylaxis
PCC	prothrombin complex concentrate
PD	pharmacodynamic
PFP	prefilled pen
PFS	prefilled syringe
PI	Prescribing Information
PK	pharmacokinetic
PKPD	pharmacokinetic and pharmacodynamic
PPK	population pharmacokinetic
PPX	prophylaxis
PRO	patient-reported outcome
PSP	primary safety population
PT	preferred term
QW	weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SEE	substantial evidence of effectiveness
SOC	system organ class
TEAE	treatment-emergent adverse event
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
TK	toxicokinetic(s)
TMDD	target-mediated drug disposition
TSS	transformed scale score
ULN	upper limit of normal
USPI	United States Prescribing Information
VPC	visual predictive check
WRO	Written Request Only

I. Executive Summary

1. Summary of Regulatory Action

On October 11, 2023, Pfizer, Inc, submitted a new BLA for marstacimab for the following indications: HYMPAVZI is a tissue factor pathway inhibitor (TFPI)-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A (HA) (congenital factor VIII deficiency) without factor VIII inhibitors and hemophilia B (HB) (congenital factor IX deficiency) without factor IX inhibitors.

On May 18, 2016, marstacimab received orphan drug designation for treatment of Hemophilia A and Hemophilia B patients with or without inhibitors. Fast Track Designation was granted on September 17, 2019.

The Applicant submitted results from one adequate and well-controlled clinical study (Study B7841005) that served as the equivalent of two studies, which provides substantial evidence of effectiveness (SEE) of marstacimab for the indication. Study B7841005 is an open-label, multi-center, two phase (observation and active treatment) study of marstacimab in patients aged 12 years and above with severe HA and moderately severe to severe HB with or without inhibitors. Participants were enrolled to independent cohorts based on presence or absence of inhibitor and treatment regimen at the time of enrollment (on-demand or prophylaxis factor replacement). The efficacy of marstacimab was based on the results from the noninhibitor cohort, observational phase on-demand (OP-OD), comprising participants who received factor on demand prior to enrollment and during the 6-month OP and cohort observational phase prophylaxis (OP-PPX), comprising participants who received prophylaxis with factor prior to enrollment and during the 6-month observation period. Following the OP, all participants received 12 months of marstacimab prophylaxis during the active treatment phase (ATP). For each cohort, the study compared treatment with factor-replacement therapy during OP with that of marstacimab prophylaxis treatment during ATP.

Marstacimab prophylaxis demonstrated superiority over on-demand factor replacement (Cohort OP-OD) and noninferiority to prophylaxis with factor (Cohort OP-PPX) based on the annualized bleeding rate (ABR) of targeted bleeds (primary endpoint), spontaneous, joint, total, and target joint bleeds (secondary endpoints), in participants with HA and HB without inhibitor. An ABR endpoint has been used to support approval for products to treat bleeding events due to hemophilia in the past. Prevention of bleeding is considered of clinical benefit, by reducing the morbidity and mortality associated with hemophilia, including joint damage and stroke.

The safety profile of marstacimab prophylaxis was determined to be acceptable for the proposed indication, and toxicities can be addressed in labeling. Enhanced pharmacovigilance is recommended for thromboembolic events based on the mechanism of action of marstacimab and the small size of the clinical studies.

BLA 761369

HYMPAVZI (marstacimab-hncq) injection

This application was reviewed by a multidisciplinary team. Clinical, clinical pharmacology, statistical, nonclinical, and product quality review teams recommended approval of marstacimab in adults and pediatric patients 12 years of age and older with hemophilia A or B without inhibitor, and in adults and pediatric patients 12 years of age and older with HA without factor and HB without factor IX inhibitors.

The overall benefit-risk is favorable as described in the Benefit-Risk Framework ([Table 2](#)) below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this interdisciplinary assessment document and the product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Hemophilia A (HA) is an X-linked recessive disorder caused by mutations in the FVIII gene which results in a severe deficiency or absence of the clotting protein factor VIII. HA occurs in approximately 1 in 5000 live male births. Patients are typically diagnosed in infancy. Patients are at increased risk for minor and serious bleeding, including life threatening spontaneous or traumatic bleeding. Disease manifestations include mucosal bleeding, easy bruising, soft tissue and muscle bleeds, hemarthrosis, and excessive bleeding with procedures or trauma. Bleeding can also occur in vital organs (including the brain if left untreated), recurrent bleeding can lead to damage in skeletal muscles and joints, causing progressive and debilitating arthropathy, resulting joint dysfunction, and decreased quality of life. Adults commonly experience hemophilic arthropathy due to recurrent joint bleeds, which is associated with significant disease morbidity. - Hemophilia B (HB) is an X-linked recessive disorder caused by mutations in the FIX gene, which results in a severe deficiency or absence of the clotting protein factor IX. HB occurs in approximately 1 in 30,000 live male births. Deficient factor IX levels result in an increased risk for minor and serious bleeding, including life threatening spontaneous or traumatic bleeding. Disease manifestations of HB are the same as HA described in the text above. - One complication of HA and HB is the development of inhibitors to factors, which is a risk associated with the use of factor replacement. Approximately 30%-35% of patients with HA and 5%-15% of patients with HB develop inhibitors. Patients with inhibitors often experience increased disease morbidity and mortality because the bleeding is more difficult to prevent or treat.	Hemophilia A (congenital factor VIII deficiency) without inhibitors and hemophilia B (congenital factor IX deficiency) without inhibitors are serious chronic diseases with significant morbidity and morality due to bleeding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- The goal of treatment in hemophilia is to prevent bleeding, improve joint function, relieve pain, and to assist the patient in continuing/resuming normal activities of daily living. - Current treatment options for patients with hemophilia A or B without inhibitors include, either episodic IV infusion of the missing factor (FVIII or FIX) in response to symptoms of a bleed (“on-demand”) or scheduled prophylactic factor (FVIII or FIX) administration to prevent bleeds from occurring. - Prophylactic treatment in patients with severe hemophilia with replacement factor, VIII or IX, has been proven to reduce the frequency of bleeding events and joint destruction in patients with hemophilia; however, it requires lifelong IV infusion every 1 to 2 weeks resulting in treatment burden, incomplete adherence, and complications associated with indwelling catheters (i.e., infection, thrombosis). - Antibodies or inhibitors develop with exposure to exogenous factor and block the activity of factor VIII or IX. Approximately 30% and 1 to 15% of patients with hemophilia A and B, respectively, will develop neutralizing alloantibodies (inhibitors) against infused FVIII or FIX. - Emicizumab (Hemlibra) is a bispecific factor IXa and factor X-directed antibody which was FDA approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with HA with or without inhibitor.	The effectiveness of the available therapy for prophylactic treatment of bleeds varies. There is a need for more effective therapy. Treatment with factor replacement can result in significant treatment burden, including need for IV catheters, risks of infection and thrombosis, and the development of inhibitors There is no approved nonfactor-based prophylactic treatment for patients with hemophilia B without inhibitors.
Benefit	- Pivotal Phase 3 Study B7841005 - Study B7841005 is an open-label, multi-center, multi-cohort, two-phase study (observational phase [OP] and active treatment phase [ATP] in adult and pediatric (aged 12 years and older and ≥35 kg) male participants with severe hemophilia A (HA) or severe hemophilia B (HB) with or without FVIII or FIX inhibitors. Participants were enrolled to independent cohorts based on the presence or absence of inhibitor and treatment regimen they were receiving for at least 6 months prior to enrollment, i.e., factor on-demand (OD) or factor prophylaxis (PPX).	The benefit of marstacimab for the treatment of patients with with severe HA or HB without inhibitors was demonstrated in two independent cohorts of Study B7841005. In the on-demand cohort, prophylatic treatment with weekly marstacimab reduced spontaneous and traumatic bleeding episodes compared to factor on-demand. This was evidenced by a lower rate of bleeding events (annualized) when participants were treated with marstacimab prophylaxis compared to treatment with factor on-demand. In the prophylaxis cohort, prophylaxis marstacimab was noninferior to treatment with factor prophylaxis for the prevention of bleeding events. This was

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The efficacy of marstacimab in patients with HA or HB without inhibitors was established based on 116 adult and pediatric participants with HA or HB without inhibitors enrolled in the two noninhibitor cohorts of Study B7841005. During the OP, participants received for 6 months the same factor treatment regimen they were on at the time of enrollment (OD or PPX) and then all participants received marstacimab prophylaxis during the 12 month ATP. The primary endpoint was annualized bleeding rate (ABR) of treated bleeding events. - Cohort OP-OD enrolled a total of 33 participants who received factor on-demand (FVIII or FIX) during 6 month OP followed by 12 month ATP with marstacimab prophylaxis. - Superiority of marstacimab prophylaxis over factor on-demand was demonstrated for the primary endpoint with an ABR treated bleeds of 3.18 with 95% CI (2.09, 4.85) during the ATP while receiving marstacimab prophylaxis and an ABR treated bleeds of 38 with 95% CI (31.03, 46.54) during OP receiving factor on-demand. The estimated ABR ratio vs. OD was 0.084 with 95% CI (0.059, 0.119), $p < 0.0001$. - Superiority was also demonstrated for all ABR based key secondary endpoints: - ABR spontaneous bleeds (ATP-ABR =2.44 [95% CI: 1.61, 3.69]; OP-ABR =30.93 [95% CI: 24.12, 39.67]; Ratio vs. OD=0.079 [95% CI: 0.054, 0.114], $p < 0.0001$) - ABR Joint bleeds (ATP-ABR =2.83 [95% CI: 1.81, 4.44]; OP-ABR =32.86 [95% CI: 26.15, 41.29]; Ratio vs. OD =0.086 [95% CI: 0.059, 0.125], $p < 0.0001$) - ABR total bleeds (ATP-ABR =7.39 [95% CI: 5.08, 10.74]; OP-ABR =47.76 [95% CI: 39.60, 57.60]; Ratio vs. OD =0.155 [95% CI: 0.116, 0.207], $p < 0.0001$) - ABR target joint bleeds (ATP-ABR =1.84 [95% CI: 1.06, 3.17]; OP-ABR 23.18 [95% CI: 17.20, 31.24]; Ratio vs. OD =0.079 [95% CI: 0.051, 0.124], $p < 0.0001$) - Superiority was not demonstrated on Physical health domain in the Hematology A Quality of Life (Haem-A-QoL) questionnaire at 6 months, as the results were not statistically significant.	evidenced by similar rates of spontaneous and traumatic bleeding when participants were treated with factor prophylaxis compared to treatment with marstacimab prophylaxis. These conclusions were based on the primary endpoint of ABR treated bleeds and on the key secondary ABR endpoints of spontaneous bleeds, joint bleeds, total bleeds, target joint bleeds. The prevention of bleeding is a clinical benefit, reducing the morbidity and mortality associated with hemophilia, including joint damage and stroke. Substantial evidence of effectiveness of marstacimab was based on one adequate and well-controlled study that served as two adequate and well controlled studies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Cohort OP-PPX enrolled a total of 83 participants who previously received factor (FVIII or FIX) prophylaxis during 6 month OP followed by 12 month ATP with marstacimab prophylaxis. – Noninferiority of marstacimab prophylaxis over factor prophylaxis was demonstrated for the primary endpoint with an ABR treated bleeds of 5.08 with 95% CI (3.40, 6.77) during the ATP while receiving marstacimab prophylaxis and an ABR treated bleeds of 7.85 with 95% CI (5.09, 10.61) during OP receiving factor. The differences versus factor prophylaxis is -2.77 with a 95% CI (-5.37, -0.16), meeting the prespecified criterion for establishing noninferiority. – Noninferiority was also demonstrated for all ABR-based key secondary endpoints with all meeting prespecified noninferiority margins. ▪ ABR spontaneous bleeds (ATP-ABR =3.78 [95% CI: 2.25, 5.31]; OP-ABR =5.86 [95% CI: 3.54, 8.19]; difference vs. factor prophylaxis=-2.087 [95% CI: -4.232, 0.060]) ▪ ABR Joint bleeds (ATP-ABR =4.13 [95% CI: 2.59, 5.67]; OP-ABR =5.66 [95% CI: 3.33, 7.98]; difference vs. factor prophylaxis=-1.527 [95% CI: -3.698, 0.644]) ▪ ABR total bleeds (ATP-ABR =5.97 [95% CI: 4.13, 7.81]; OP-ABR =8.84 [95% CI: 5.97, 11.72]; difference vs. factor prophylaxis =2.868 [95% CI: -5.613, -0.122]) ▪ ABR target joint bleeds (ATP-ABR =2.51 [95% CI: 1.25, 3.76]; OP-ABR =3.36 [95% CI: 1.59, 5.14]; difference vs. factor prophylaxis=-0.856 [95% CI: -2.413, 0.701]) – Noninferiority for physical health domain in Haem-A-QoL at 6 months could not be tested due to rules of hierarchical testing.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	Overall Safety Findings • The review of safety focused Study B7841005 and events that occurred during the ATP while participants were receiving marstacimab. Data from the two cohorts were pooled and the safety population comprised 116 adolescent and adult participants with HA or HB without inhibitors who received at least one dose of open-label marstacimab prophylaxis during the ATP period. • The key safety findings were: – There were no fatal adverse events. – Serious adverse events (SAEs) occurred in 6% of participants; however, only one of these SAEs was assessed as related to marstacimab, peripheral swelling of the right calf. – Adverse events leading to permanent discontinuation of marstacimab occurred in only 2 (2%) participants. One participant discontinued treatment due to atypical meningioma, assessed as not related, and another discontinued due to peripheral swelling, assessed as related. – Treatment-emergent adverse events (TEAEs) were reported in 64% of participants while receiving marstacimab prophylaxis during the ATP. The most common TEAEs, occurring in ≥5% of participants, were viral infection (21%), local administration reactions (10%), hemorrhage (10%), nasopharyngitis (9%), headache (7%) and pruritus (7%). The most frequently reported adverse reaction observed in ≥10% of participants while receiving marstacimab with marstacimab were injection site reactions. • Thromboembolic events are an adverse event of special interest based on the mechanism of action of marstacimab. – In Study B7841005, there were no events of thrombosis reported in participant while receiving marstacimab during the ATP. – There was 1 case of a thromboembolic event (pulmonary embolism and DVT) reported in a healthy participant who received marstacimab on a clinical study.	The safety data submitted were sufficient to characterize the toxicity profile of marstacimab. Although all data was uncontrolled, this was acceptable given the rarity of the disease, clear mechanism of action, and experience with other hemophilia drugs. Overall the marstacimab was well tolerated. The risks of marstacimab are generally comparable to those of other anti-hemophilic treatments used for prophylactic treatment for patients with hemophilia. The identified risk of hypersensitivity and the class risk of thromboembolism should be included in the Warnings and Precautions section of the USPI. Although there were no reports of thromboembolic events in the pivotal study, given the mechanism of action of marstacimab and the limited size of the safety database, the review team recommends enhanced pharmacovigilance for the risk of thromboembolic events.

Source: FDA table

Abbreviations: CI, confidence interval; DVT, deep vein thrombosis; FVIII, factor VIII; FIX: factor IX;USPI, United States Prescribing Information; vs., versus

2.2. Conclusions Regarding Benefit-Risk

BLA 761369, marstacimab, provided substantial evidence of effectiveness from one adequate and well-controlled study with two cohorts that serves as the equivalent of two studies. The benefit-risk profile is favorable, and all disciplines recommend approval. Hemophilia (A or B) are rare and serious diseases with limited treatment options depending upon the subtype. If left untreated, hemophilia will result in significant morbidity and early mortality from uncontrolled bleeding arising spontaneously, following injury, or related to surgery. In general, affected patients start on a life-long treatment program of blood products or recombinant factor concentrates designed to “bypass” the absent clotting factor, but this treatment carries the burden of frequent intravenous (IV) administration, risks of infection and thrombosis, and risk for development of inhibitors which can result in decreased or ineffective treatment. Additional available therapy includes a nonfactor therapy, emicizumab, to prevent severe bleeding for patients with HA with and without inhibitors.

Marstacimab treatment provides a prophylaxis treatment for patients with congenital hemophilia A or B without inhibitors. For the subgroup of congenital HB without inhibitors, this product has the potential to address an unmet medical need because there is no available nonfactor replacement therapy for this subgroup. The nonclinical, clinical, statistical, and clinical pharmacology teams support the approval based on the nonclinical and clinical data packages and did not identify any deficiencies. No important differences of opinion were voiced during the review process.

The clinical data package consists of a single study with two cohorts that served as two adequate and well-controlled studies that demonstrated an effect on ABR, an endpoint that has been used for the approval of other monoclonal antibodies or blood products for the treatment of hemophilia. The prevention of bleeding, a clinical benefit, is expected to reduce the morbidity and mortality associated with hemophilia, including joint damage and stroke.

Study B7851005 is an open-label, multi-center, two phase (observation and active treatment) study of marstacimab in participants aged 12 years and older with severe HA and moderately severe to severe HB, with or without inhibitors. The study was designed to allow comparison of ABRs during the 6-month observation period, during which participants received the same treatment regimen they were receiving at the time of enrollment, on-demand or prophylaxis with factor, with ABRs during the ATP with marstacimab prophylaxis. The two noninhibitor cohorts formed the basis of establishing SEE in this application.

In Cohort OP-OD, the effectiveness of marstacimab was established by demonstrating superiority of ABR during prophylaxis with marstacimab over on-demand treatment with factor. The mean ABR of treated bleeding for marstacimab prophylaxis was 3.18 (95% CI: 2.09, 4.85) bleeds compared to 38 (95% CI: 31.03, 46.54) bleeds for the on-demand factor.

In Cohort OP-PPX, the effectiveness of marstacimab was established by demonstrating noninferiority of ABR during prophylaxis with marstacimab compared to prophylaxis with factor. Mean ABR of treated bleeds for marstacimab prophylaxis was 5.08 (3.4, 6.77) compared to 7.85 (5.09, 10.61) for prophylaxis with factor.

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The risks of marstacimab can adequately be described in labeling. Injection site reactions, based on experience in clinical studies of marstacimab, and thromboembolic events, based on mechanism of action and risks associated with other drugs in the class, will be included in warnings and precautions of the United States Prescribing Information (USPI).

Because of the limited size of the safety database for marstacimab, enhanced pharmacovigilance will be instituted for thromboembolic events.

II. Interdisciplinary Assessment

3. Introduction

Marstacimab (proposed proprietary name, HYMPAVZI), a first-in-class, new molecular entity, is a monoclonal antibody (mAb) antagonist of endogenous tissue factor pathway inhibitor (TFPI). TFPI is 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, neutralizing the activity of TFPI may serve to enhance the extrinsic pathway and reduce or eliminate the need for replacement factor VIII (FVIII) and factor IX (FIX). Marstacimab acts independently from FVIII and FIX, and thus would not be expected to result in the formation of factor neutralizing antibodies.

The Applicant proposes the following indication: for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A (HA) (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (HB) (congenital factor IX deficiency) without factor IX inhibitors.

The proposed dosing regimen is a loading dose of 300 mg administered by subcutaneous (SC) injection on Day 1 followed by maintenance dosing starting one week later (Day 8) of 150 mg every week by SC injection. The dose may be adjusted to 300 mg SC injection weekly in patients weighing ≥ 50 kg when control of bleeding events is judged to be inadequate by the healthcare provider.

Disease Background

Congenital hemophilia is a rare X-linked bleeding disorder caused by deficiencies of FVIII in HA and FIX in HB. Patients with hemophilia can have spontaneous bleeding events and bleeding events to even minor trauma, which can affect critical organs and be fatal. Clinical hallmarks of hemophilia are joint and muscle hemorrhages, easy bruising, and prolonged and potentially fatal hemorrhage after trauma or surgery. The severity of hemophilia is correlated with residual factor levels, mild (5- <40% FVIII or FIX activity), moderate (1 to 5% FVIII or FIX activity) and severe (<1% FVIII or FIX activity) ([Srivastava et al. 2013](#)). Approximately a third of cases of hemophilia are severe.

The frequency of HA is approximately 17.1 cases in 100,000 newborn males ([Soucie et al. 2020](#)) and approximately 3.3 cases in 100,000 newborn males for HB ([Zimmerman and Valentino 2013](#)), with similar estimated incidence in the United States. In HA, the absence of functional FVIII interrupts the coagulation cascade and the ability to form a stable clot in response to trauma. The resultant bleeding complications can be severe and life threatening and can lead to long-term morbidity from joint damage due to recurrent bleeds. In 30 to 35% of patients with HA, a neutralizing antibody, known as a FVIII inhibitor, forms, rendering exogenous and endogenous FVIII nonfunctioning. Patients with FVIII inhibitors are more difficult to treat in response to bleeding events, leading to a higher rate of progressive joint disease from frequent joint bleeds and increased risk of death from uncontrolled bleeding. In HB, bleeding tendency is

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in accordance with severity of factor deficiency, and patients with severe form (FIX <1%), who account for approximately 30 to 45% of persons with HB, usually suffer from recurrent joint, soft-tissue and muscle bleeding. The reported rate of FIX inhibitors is 1 to 15% of all patients with HB ([Male et al. 2021](#)).

Patients with HA and HB are typically treated with blood/recombinant factor concentrates which supply the necessary missing clotting factors. The goal of treatment in hemophilia is to prevent or minimize the occurrence of bleeding to improve joint function, alleviate pain, and help the patient to continue/resume regular daily activities. However, up to 32% of patients with severe HA and 5% of patients with severe HB develop neutralizing antibodies to the administered factors rendering the factor concentrates ineffective to prevent bleeding events. The patients who have hemophilia and inhibitors are then treated with a bypassing strategy designed to overcome the missing factor and inhibitor.

Treatment with replacement factor can either be in response to a bleeding event (episodic or “on demand”) or scheduled to prevent bleeds by maintaining factor levels in a protective range (prophylactic treatment). The aim of prophylaxis is to reduce FVIII or FIX deficiencies and reduced spontaneous bleeding events by maintaining factor activity of at least 1% ([Berntorp and Shapiro 2012](#)). There is significant evidence that prophylactic treatment in children with severe hemophilia helps prevent bleeding episodes and the associated joint damage that is a major morbidity in patients with hemophilia ([Manco-Johnson et al. 2007](#)). In adults with severe hemophilia, an early start of treatment with long-term prophylaxis is reported to reduce bleeding frequency and subsequent chronic joint disease and result in better quality of life ([Khawaji et al. 2011](#)). The choice of regimens (i.e., on-demand or prophylaxis with factor) is multi-factorial and may be based on frequency and severity of bleeding, patient preference and lifestyle, and regional/geographic standard of care. In resource-rich countries, prophylactic treatment initiated prior to any joint bleeds is preferred.

Over the past 50 years, the treatment options for hemophilia have advanced. Initial outcomes measures were focused on raising the factor activity levels. With the incorporation of prophylactic therapy, annualized bleeding rate (ABR) became the primary outcome measure ([Konkle et al. 2019](#)). Bleeding rates can be impacted by several patient-specific factors as well as external factors, such as clotting factor level, age, overall health, activity level, and seasonality. There can be some subjectivity with measurement of ABR as the patient and treating physician must each define what constitutes a bleeding event; ABR generally only measures recognized bleeding events and may not capture subclinical bleeds. Overall, ABR is a clinically meaningful endpoint as a reduction in bleeding events is important to patients by decreasing risk of mortality, organ and tissue damage, including joint damage, which is associated with recurrent bleeds, and allowing greater activity that might otherwise be limited due to risk of trauma and bleeding.

Current Therapy Options

The current treatment options for patients with hemophilia A or B without inhibitors include:

- (1) Replacement of missing FVIII or FIX can be used as an episodic intravenous (IV) infusion of the missing factor (FVIII or FIX) in response to symptoms of a bleed “on-demand” or scheduled routine prophylactic FVIII or FIX administration to prevent bleeds from occurring. Prophylactic treatment with replacement factors VIII or IX has proven to reduce the frequency of bleeding events; however, it requires lifelong IV infusion every 1 to 2 weeks resulting in treatment burden, incomplete adherence, and complications associated with indwelling catheters (i.e., infection, thrombosis). There are two type of replacement factors therapy:
 - (a) plasma-derived factors concentrate which have short half 1 to 2 days and require frequent IV injections at based on body-mass–dependent doses.
 - (b) recombinant factor concentrates which have longer half-life of 1 to 2 weeks.
- (2) Hemlibra (emicizumab-kxwh) SC injection is a bispecific FIXa-and factor X (FX)-directed antibody, which was approved by FDA on November 16, 2017, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with HA with inhibitors. Hemlibra was approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with HA without FVIII inhibitors in 2018. The recommended loading dose of emicizumab is 3 mg/kg administered by SC injection once weekly for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg once very week, or 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks. The emicizumab product label contains a boxed warning that states cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving emicizumab prophylaxis. The boxed warning contains the recommendation to monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered, and to discontinue aPCC and suspend dosing of emicizumab if symptoms occur.
- (3) Gene therapy: Gene therapy achieved by infusion of a recombinant, adeno-associated virus–based vector containing the gene for the missing coagulation factor therapy (i.e., Hemgenix for HB and ROCTAVIAN for HA).

The World Federation of Hemophilia (WFH) strongly recommends prophylactic treatment for patients with hemophilia A or B with a severe phenotype sufficient to prevent bleeds at all times. Prophylaxis should be individualized (adjusting prophylaxis dose/frequency or both), taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference ([Srivastava et al. 2020](#)).

Marstacimab is a first-in-class TFPI antagonist with a mechanism of action that is different than the other available nonfactor product therapy and provides for an alternative nonfactor treatment option for patients with HA and HB without inhibitors. Marstacimab is the first nonfactor replacement therapy that will be available for patients with HB without inhibitors, which addresses an unmet medical need.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. The ATP ABR Point Estimates and 95 % CI in Hemophilia B Compared to Hemophilia A in Cohort OP-PPX

3.1.2. Key Safety Review Issues

No safety review issues were found.

3.2. Approach to the Clinical Review

The early phase studies, summarized in Section [14](#), assessed the bioequivalence, pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of different dosing regimens and provided preliminary safety, immunogenicity, and tolerability of marstacimab.

[Table 3](#) provides an overview of the clinical studies conducted to support the benefit-risk assessment of marstacimab for participants with HA and HB without inhibitors. Results from two independent cohorts of participants with HA and HA without inhibitor from the pivotal study, Study 7841005 (Cohort OP-OD and Cohort OP-PPD) formed the basis of the assessment of benefit. The assessment of benefit was based on a comparison of efficacy data from the active treatment phase (ATP), during which all participants received marstacimab, and efficacy data from the OP, during which participants received treatment based on their cohort assignment (factor on-demand factor or factor prophylaxis).

The assessment of risk was based primarily on data derived from Study 7841005 during 12-month ATP period with marstacimab prophylaxis along with analysis of safety data from long-term open-label study (Study B7841007) as well as a pooled safety set comprising all adverse events occurring in participants with HA or HB with or without inhibitor occurred while receiving marstacimab on a clinical study.

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Marstacimab

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
B7841005 (BASIS)	Adolescent and adults between 12 to <75 years of age with severe hemophilia A or moderately severe to severe hemophilia B (defined as FVIII activity <1%, or FIX activity ≤2%, respectively) with or without inhibitors	• Control type: None • Randomization: None • Blinding: Open label • Biomarkers: None • Innovative design features: One-way, open-label, multicenter, 2-phase study of 6-month observational phase (OP), followed by single arm 1-year active treatment phase (ATP).	• Drug: marstacimab • Dosage: 300 mg SC for initial dose followed by 150 mg SC QW. • Number treated: OP 128/ATP 118 • Duration (quantity and units): Treatment: 6-month OP; 12-month ATP.	• Primary: annualized bleeding rate (ABR) of treated bleeding events • Secondary: ABR of treated bleeding events with respect to comparisons with prior on demand or prophylactic therapy for regions outside EU	Planned: 179	• Centers: 52 • Countries: 19

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
B7841002	Participants with severe hemophilia	- Control Type: None - Randomization: None - Randomization Ratio: NA - Blinding: Open-label - Biomarkers: None - Innovative design features: None	- Drug (established name): marstacimab - Dose: - Cohort 1: 300 mg SC QW - Cohort 2: 300 mg SC loading dose, 150 mg SC QW - Cohort 3: 450 mg SC QW - Cohort 4: 300 mg SC QW - Number treated: 26 - Duration (quantity and units): 3 months with a 1-month follow-up	- Primary: Frequency, severity, and causal relationship of TEAEs and withdrawals due to TEAEs; Day 1 up to Day 113 - Secondary: Frequency and annualized rate of bleeding episodes; Day 1 up to Day 85	Planned: 38	- Centers: 8 - Countries: 5
B7841003	Participants with severe hemophilia	- Control Type: None - Randomization: None - Randomization Ratio: NA - Blinding: Open-label, long-term study - Biomarkers: None - Innovative design features: None	- Drug (established name): marstacimab - Dose: 300 mg SC QW or 150 mg QW - Number treated: 20 - Duration (quantity and units): Up to 365 days with a 1-month follow-up	- Primary: Frequency, severity and causal relationship of TEAEs; Day 1 up to Day 393. - Secondary: Frequency and annualized rate of bleeding episodes; Day 1 up to Day 393.	Planned: 24	- Centers: 11 - Countries: 9

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized ²	Number of Centers and Countries
B7841007	Participants who completed Studies B7841005 or B7841008	- Control Type: None - Randomization: None - Randomization Ratio: NA - Blinding: Open-label, long term - Biomarkers: None - Innovative design features: None	- Drug (established name): marstacimab - Dose: 150 mg SC QW - Number treated: 87 - Duration (quantity and units): Until marstacimab is commercially available in each country or when participant has completed 7 years in the study with a 28- to 35-day follow-up period.	Primary: ABR of treated bleeding events.	Planned 88	- Centers: 36 - Countries: 14

Source: Reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.² If no randomization, then replace with "Actual Enrolled."

Abbreviations: EU, European Union; FIX, factor IX; FVIII, factor VIII; NA, not applicable; NCT, national clinical trial; QW, once weekly; SC, subcutaneous

4. Patient Experience Data

The patient-reported outcome (PRO) endpoint failed to demonstrate superiority over factor on demand (Section [6.2.1.5.1.1](#)). Analysis of PRO endpoint for noninferiority over factor prophylaxis could not be tested due to rules of hierarchical testing (See Section [6.2.1.5.2.1](#)).

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

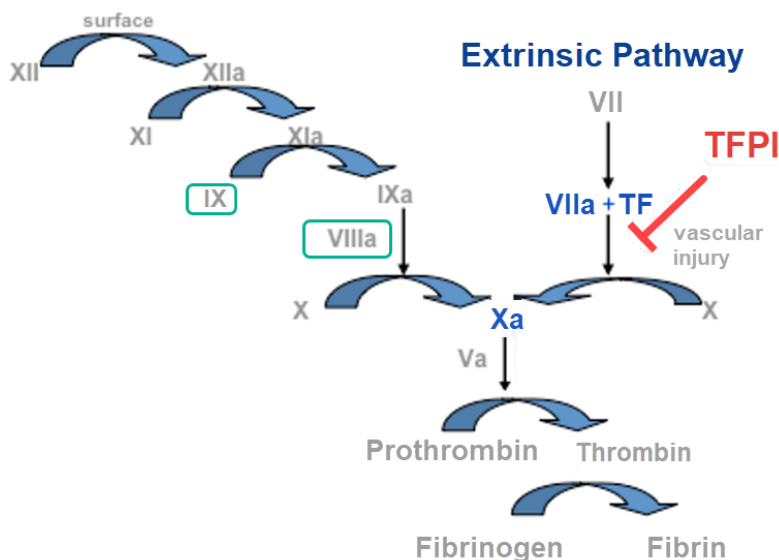
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Marstacimab is an immunoglobulin G1 (IgG1) mAb TFPI antagonist designed to prevent bleeding by enhancing the extrinsic coagulation pathway in patients with hemophilia (A and B). Both conditions are inherited X-linked genetic disorders that occur almost exclusively in males. Only rare instances have been reported in females where both X chromosomes are affected or if one X chromosome is affected and the other X chromosome is absent or nonfunctional.

Patients with HA and HB are susceptible to bleeding due to deficiency in factor VIII and factor IX, respectively (see [Figure 1](#)). Deficiencies in coagulation factor IX (HB) or factor VIII (HA) of the intrinsic pathway can prevent thrombin formation causing downstream inhibition of the coagulation cascade in hemophilia patients, which may result in excessive bleeding.

Figure 1. Intrinsic and Extrinsic Coagulation Pathway
Intrinsic Pathway



Source: Modified Applicant figure

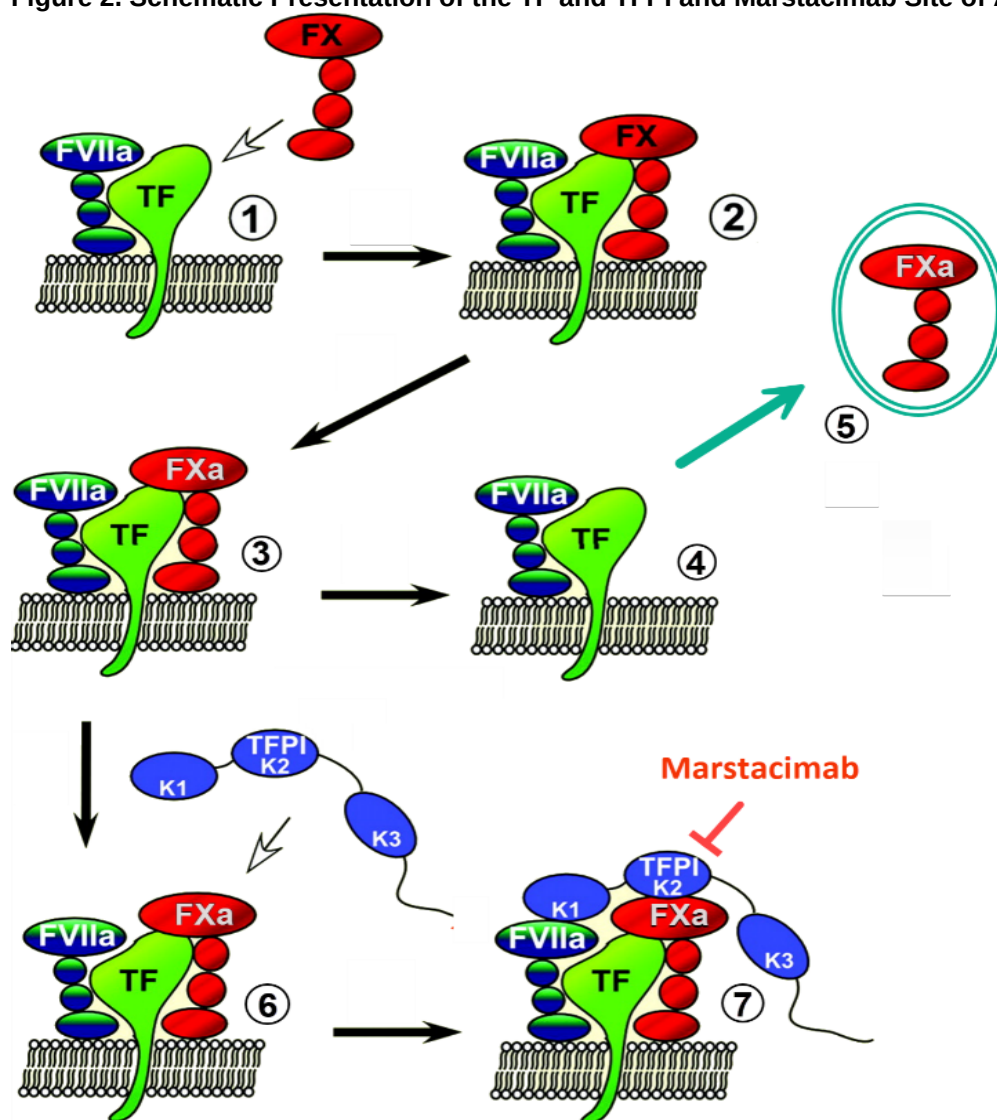
Abbreviations: TF: tissue factor; TFPI: tissue factor pathway inhibitor

Tissue factor (TF)¹ is an extrinsic coagulation protein released in response to extravascular cell damage that enhances FVII and FX, independent of intrinsic coagulation pathway. Thus, strategies to increase TF activity might enhance coagulation in both HA and HB.

Normally, TF activity is negatively regulated by TFPI² (shown in [Figure 1](#) in red). The role of TF and TFPI in the extrinsic coagulation pathway is depicted in [Figure 2](#). TFPI is an endogenous serine protease inhibitor containing at least three known Kunitz-type domains (K1, K2 and K3) separated by short stretches of amino acids. Marstacimab binds to TFPI Kunitz 2 (K2) domain, preventing TFPI from inhibiting TF.

¹ TF is an integral membrane bound blood coagulation protein expressed in many cells in organs such as lungs, brain, heart, testes, uterus, and placenta. Vascular tissue injury or disruption in endovascular activity, can trigger TF/FVIIa/FXa complex to promote and activate the extrinsic coagulation pathway, enhancing the conversion of prothrombin to thrombin and consequently formation of blood clot at the site of injury.

² TFPI is an endogenous protease inhibitor produced by the endothelial cells of the vascular smooth muscle cells and several blood cells (i.e., megakaryocytes/ platelets, monocyte) that circulates in plasma. There are two known isomers of TFPI (TFPI α and TFPI β). TFPI α is the full-length isoform consisting of three Kunitz-type-domains K1, K2, and K3, the latest not bearing inhibitory function. The anticoagulant action of TFPI is proposed to occur in a two-stage process. Release of K2 binds FXa and inactivates it followed by K1 binding to TF-FVIIa complex that prevents further activation of Factor X ([Price et al. 2004](#)).

Figure 2. Schematic Presentation of the TF and TFPI and Marstacimab Site of Action

Source: Modified figure from [Crawley and Lane \(2008\)](#)

Abbreviations: FVIIa, factor VIIa; FX, factor X; FXa, factor Xa; TF, tissue factor; TFPI, tissue factor pathway inhibitor

As depicted in [Figure 2](#), the extrinsic clotting pathway is normally triggered by TF in response to tissue injury (1), which forms a complex with FVIIa and FX (2), activating (3) and releasing FXa (4) into the surrounding tissue to (5) promote coagulation via the common coagulation pathway, leading to increased thrombin and blood clotting at the site of injury (see [Figure 1](#). Intrinsic and Extrinsic Coagulation Pathway). Plasma TFPI regulates (blocks) the FVIIa/TF/FXa complex (6), inhibiting TF from promoting and activating FX. TFPI binding to the FVIIa/TF/FXa complex occurs via its K2 and K1 domains. Marstacimab binds and inhibits plasma TFPI via the K2 domain (7), which increases the activity of TF and the pro-coagulatory function of FXa.

To establish proof of concept for marstacimab as a potential treatment for HA and HB, a series of in vitro and in vivo pharmacology studies were conducted by the Applicant, as discussed in Sections [5.1.1](#) to [5.1.3](#) below. These data demonstrated that marstacimab binds and inhibits the combined K1K2 domains (via K2) of TFPI from humans and nonclinical species. The results of

these studies establish a therapeutic rationale for marstacimab to enhance extrinsic coagulation pathway as a treatment for patients with hemophilia A and B.

5.1.1. In Vitro Characterization of Marstacimab-TFPI Interaction

Marstacimab binds and inhibits human and animal TFPI. Marstacimab has high affinity to human TFPI K2 ($K_d = 2.63 \pm 0.08 \text{ nM}$) and the combined K1K2 domains ($7.9 \pm 0.33 \text{ nM}$) but does not bind to the K1 domain of TFPI. In a cross-reactivity study, marstacimab was shown to have a similar inhibitory effect on TFPI K1K2 domains across different species, suggesting their relevance to evaluating the clinical utility (and safety) of marstacimab ([Table 5](#)). With no binding to K1, the procoagulant activity of marstacimab is related solely to binding and inhibition of TFPI's K2 and K1K2 domains.

Table 5. Marstacimab In Vitro Dissociation Constant (K_d) for TFPI K1K2 Domains in Human and Pharmacologically Relevant Animal Species

Species	TFPI K1K2 Domains, nM
Human	3.7 ± 0.28^1
Monkey	1.22 ± 0.03
Mouse	0.58 ± 0.05
Rabbit	4.25 ± 0.05
Rat	1.57 ± 0.04

Source: Reviewer constructed summary table from Surface Plasma Resonance study

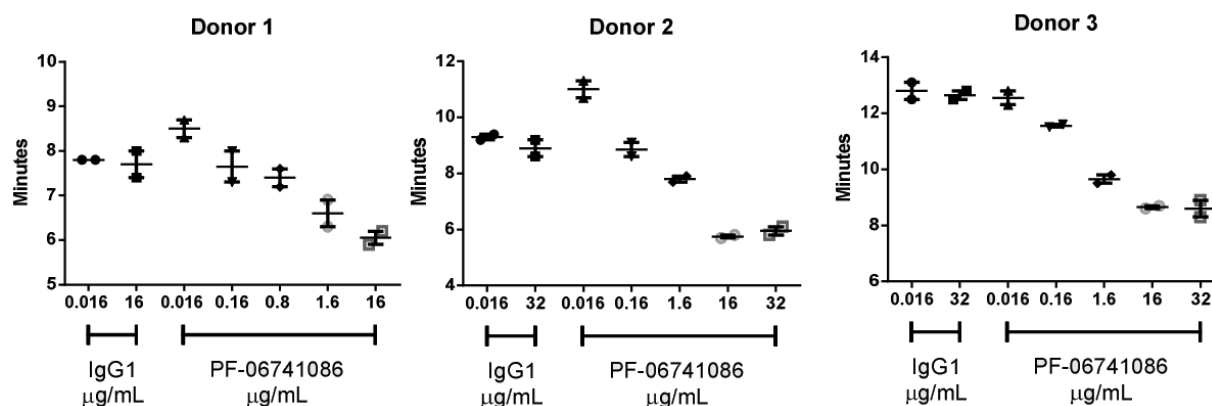
¹ Differences in K_d for human K1K2 were considered minimal within 2-fold.

Abbreviations: K1, Kunitz domain 1; K2, Kunitz domain 2; TFPI, tissue factor pathway inhibitor

5.1.2. In Vitro Pharmacological Activity of Marstacimab

The pharmacological activity of marstacimab was evaluated in a series of in vitro studies. In a cell-free enzymatic assay, marstacimab dose-dependently inhibited the combined K1K2 domains of TFPI to generate active FX with a half-maximal effective concentration (EC_{50}) of 1312 ng/mL and increased the combined activity of the FXa and FVIIa/TF/FXa with an EC_{50} of 1985 ng/mL.

Marstacimab's ability to enhance clot formation was demonstrated using normal whole blood. Marstacimab significantly reduced clotting time (accelerated clot formation) in whole blood from various donors ([Figure 3](#)).

Figure 3. Dose-Dependent Decrease in Clotting Time by Marstacimab Using Whole Blood

Source: Applicant-provided figures

Abbreviation: IgG1, immunoglobulin G1; PF-06741086, marstacimab

The effect of marstacimab on diluted prothrombin time (dPT) and activated partial thromboplastin time (aPTT) as measures of clotting time was evaluated using human plasma from healthy donors. As expected, marstacimab dose-dependently shortened dPT, a marker of extrinsic and common pathway integrity but not aPTT, a marker of intrinsic and common pathway integrity.

A summary of in vitro pharmacology studies is described in [Table 6](#). Collectively, in vitro studies show marstacimab is effective in inhibiting and neutralizing TFPI, increasing free FXa, reducing clotting time in whole blood, and enhancing thrombin generation in platelet-poor plasma.

Table 6. Characterization of Marstacimab In Vitro Pharmacological Activity

Assay	Result ($\mu\text{g/mL}$)	Conclusion
Direct FXa activity ¹	$\text{EC}_{50}=1.3$	Marstacimab dose-dependently inhibited TFPI with effective concentrations in a clinically relevant range
Combined FXa+FVIIa/TF/FXa activity ²	$\text{EC}_{50}=2.0$	
	$\text{C}_{\text{avg,ss}}=6.5$	
Clotting times ³ in plasma from:		Marstacimab activated the extrinsic pathway (dPT), but not the intrinsic pathway (aPTT)
Humans (dPT)	$\text{EC}_{50}=406\text{nM}$	
Rabbits (dPT)	$\text{EC}_{50}=629\text{nM}$	
Monkeys (dPT)	$\text{EC}_{50}=273\text{nM}$	
Humans, rabbits & monkeys (aPTT)	No significant effects	Marstacimab increased thrombin levels by 94%
Thrombin generation assay ⁴	Pretreatment thrombin, 112.4nM; Post-treatment thrombin, 217.7nM	

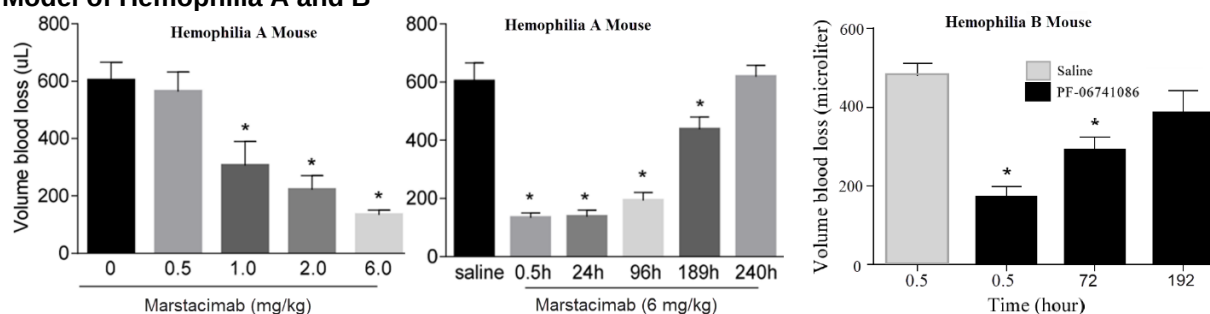
Source: Reviewer constructed summary table from Studies 08502, 142056, and 123404.

¹ Measured by enzymatic chromogenic-based assays.² Conducted using human nonhemophilic whole blood and plasma.³ Conducted using nonhemophilic plasma from different species.⁴ Conducted using human nonhemophilic citrate generated platelet-poor plasma.Abbreviations: aPTT, activated partial thromboplastin time; $\text{C}_{\text{avg,ss}}$, average plasma concentration at steady state at the MRHD; dPT, diluted prothrombin time; EC_{50} , half-maximal effective concentration; FVIIa, factor VIIa; FXa, factor Xa; TF, tissue factor; TFPI, tissue factor pathway inhibitor

5.1.3. Proof of Concept Animal Model Data

The pharmacological activity of marstacimab was evaluated in vivo in mouse models of HA (FVIII-deficient) and HB (FIX-deficient). Marstacimab dose-dependently reduced blood loss in both HA (76%) and HB (65%) mouse models relative to controls. As shown in [Figure 4](#), blood volume loss in the HA mouse model lasted up to 189 hrs (7.9 days) at a maximum dose of 6 mg/kg (a human equivalent dose of 360 mg based on body weight), which is similar to the maximum recommended once weekly human dose of 300 mg. The in vivo studies in mouse models suggest that marstacimab might increase fibrin deposition and increase platelet accumulation in hemophilia patients. A summary of the in vivo model data is shown in [Table 7](#).

Figure 4. Dose-Dependent Decrease in Blood Volume Loss and Duration of Effect in a Mouse Model of Hemophilia A and B



Source: Applicant study 135244 & 121321

Table 7. Marstacimab Effects on Clinically Relevant Endpoints in Mouse Models of Hemophilia A and B

Parameter Tested	Mouse Hemophilic Injury Models			
	Acute Tail Transection			Microvessel Laser Injury ¹
	Hemophilia A (FVIII Deficiency)	Hemophilia B (FIX Deficiency)		Hemophilia A (FVIII Deficiency)
Treatment method modeled (relative to bleed induction)	Pretreatment, 30 min	Pretreatment 30 min	After injury	Injury caused at various times
Marstacimab dose, IV (mg/kg)	0.5, 1, 2, or 6	6	6	6
Human equivalent dose (mg)	30, 60, 120, or 360	360	360	360
Effective response duration, hours	189	72	-	168
Decrease in bleeding (%) compared to control	6.1, 51, 63.2, or 77.7	65-74	60	-
Clinically relevant endpoints alleviated by marstacimab:				
Blood loss	✓	✓	-	-
↑ Fibrin deposition	-	-	✓	✓
↑ Platelet accumulation	-	-	-	✓

Source: Reviewer-constructed summary table from Study reports #121321 and 135244

¹ PD assessed using Intravital Microscopic. It provides real time imaging and quantitative measurement of fibrin deposition and platelet clot formation using fluorescently labeled antibodies directed to platelet antigen or fibrin.

✓ Denotes animal model useful for assessment of a clinically relevant endpoint.

- Denotes animal model was not used for assessment of a clinically relevant endpoint.

↑ Denotes increase (in)

Abbreviations: FIX, factor IX; FVIII, factor VIII; IV, intravenous; PD, pharmacodynamics

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In summary, in vitro and in vivo studies demonstrated marstacimab binds and inhibits K2 domain of the combined K1K2 domains of TFPI (Kd 3.7nM), but not the K1 domain. Marstacimab neutralized TFPI, increased FXa, shortened clotting time, increased thrombin generation in whole blood, and reduced blood loss in mouse models of HA and HB. The greatest effects in animal models of HA and HB were achieved at 6 mg/kg, which approximates a 360 mg marstacimab dose for a 60 kg patient. Collectively these studies support a plausible mechanism of action by which marstacimab may be a potentially effective treatment of HA and HB.

5.2. Clinical Pharmacology / Pharmacokinetics

Table 8. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Marstacimab is a tissue factor pathway inhibitor (TFPI) antagonist.
Mechanism of action	Marstacimab is a human monoclonal immunoglobulin G1 (IgG1) antibody directed against the Kunitz domain 2 (K2) of TFPI, the primary inhibitor of the extrinsic coagulation cascade. TFPI binds to and inhibits the factor Xa active site via its second Kunitz inhibitor domain (K2).
Active moieties	Humanized IgG1 monoclonal antibody
QT prolongation	A thorough QT study was not conducted in humans. QT interval in monkeys was unaffected by marstacimab doses up to 500 mg/kg/week (219-times the MRHD based on AUC).
	General Information
Bioanalysis	Plasma marstacimab concentration was quantified using a validated electrochemiluminescence (ECL) method.
Healthy subjects versus patients	Based on the population PK analysis, CL values in healthy subjects were 19.9% higher than that of patients with hemophilia. The difference is not clinically significant.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Steady state marstacimab plasma concentration (mean, %CV) following weekly SC administration of 150 mg (with 300 mg loading dose) in patients with hemophilia.

Table 9. Drug Exposure at Steady-State After Once Weekly Subcutaneous Doses

Parameter	Adults	Adolescents
Mean (%CV)		
C _{min,ss} (µg/mL)	13.7 (90.4%)	27.3 (53.2%)
C _{max,ss} (µg /mL)	17.9 (77.5%)	34.7 (48.5%)
C _{avg,ss} (µg /mL)	16.5 (81.2%)	32.1 (49.5%)

Source: Table 13 of population modeling analysis report PMAR-EQDD-B784a-DP-1331-Amendment
 Abbreviations: C_{avg,ss}, average plasma concentration at steady state; C_{max,ss}, maximum concentration at steady state; C_{min,ss}, minimum concentration at steady state; CV, coefficient of variance

Range of effective dose(s) or exposure	The starting dose of marstacimab is loading dose of 300 mg SC followed by a maintenance dose of 150 mg SC weekly. Dose may be increased to 300 mg in participants who weigh ≥50 kg if control of bleeding is inadequate.
Maximally tolerated dose or exposure	No maximum tolerated dose was identified. Highest dose studied was 450 mg SC weekly.

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Characteristic	Drug Information
Dose proportionality	Marstacimab exposure (AUC and C_{max}) increases in a greater than dose-proportional manner over the dose range of 150 mg to 450 mg.
Accumulation	Mean steady state accumulation ratio is approximately 4- to 5-fold.
Time to achieve steady-state	Steady state is achieved by approximately 60 days (8 th or 9 th SC dose) when marstacimab is administered weekly.
Bridge between to-be-marketed and clinical trial/study formulations	Both prefilled syringe (PFS) and prefilled pen (PFP) are to-be-marketed product presentations. PFS was used in the pivotal Phase 3 study (Study B7841005). Marstacimab exposure was comparable between PFS and PFP presentations based on a relative bioavailability study in healthy volunteers (Study B7841009).
Absorption	
Bioavailability	71% (SC route of administration)
T_{max}	Median 23 to 59 hours
Food effect (fed/fasted)	NA as marstacimab is administered via SC injection
Distribution	
Volume of distribution	Apparent V_d is 8.6 L in patients with hemophilia
Plasma protein binding	NA
Drug as substrate of transporters	NA as marstacimab is a monoclonal antibody
Elimination	
Mass balance results	N/A
Clearance	Marstacimab is cleared via linear and nonlinear mechanisms. Marstacimab exhibited nonlinear pharmacokinetics due to target-mediated drug disposition (TMDD) upon interaction with its target, i.e., TFPI. Once the target becomes saturated, linear pathway (i.e., catabolism) dominates.
Half-life	Based on population PK analysis, median time for 50% of marstacimab to be eliminated is approximately 7 and 10 days and median time for 90% of marstacimab is eliminated 14 and 22 days, for 150 mg and 300 mg dose, respectively. A typical elimination half-life is not provided as marstacimab elimination involves both linear and nonlinear clearance mechanisms.
Metabolic pathway(s)	Marstacimab is expected to be metabolized into small peptides by catabolic pathways
Primary excretion pathways (% dose)	NA
Intrinsic Factors and Specific Populations	
Body weight	Body weight was a significant covariate impacting the pharmacokinetics of marstacimab. Marstacimab exposures over the body weight range 35-120 kg show a trend for increase in exposure with decrease in body weight. However, dose adjustment based on body weight is not required.
Age	Based on the population PK analysis, after accounting for the weight difference, there was minimal difference (3.1%) in CL for adolescents (12 to <18 years old) and adults.
Renal impairment	No dedicated study has been conducted to evaluate the impact of renal impairment. As marstacimab is a monoclonal antibody, pharmacokinetics are not expected to be different in patients with renal impairment.
Hepatic impairment	No dedicated study has been conducted to evaluate the impact of hepatic impairment. As marstacimab is a monoclonal antibody, pharmacokinetics are not expected to be different in patients with hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	NA as marstacimab is a monoclonal antibody

Characteristic	Drug Information
Inhibition/induction of transporter systems	NA as marstacimab is a monoclonal antibody
	<i>Immunogenicity (if Applicable)</i>
Bioanalysis	ADAs against marstacimab were assayed using an ECL bridging immunoassay and NAb were detected using a neutralizing anti-marstacimab competitive ligand binding ECL NAb assay. The ADA and NAb assays were evaluated by Dr. Jee Chung and was found to be acceptable.
Incidence	In the pivotal Phase 3 study (Study B7841005), 23 participants developed ADA (19.8%) and out of 23 ADA-positive participants, 6 participants developed NAb (26%).
Clinical impact	Participants who received marstacimab and developed anti-marstacimab antibodies had reduced marstacimab concentrations, geometric mean decrease in the range of 24% to 50%, compared to those who did not develop anti-marstacimab antibodies through the course of the treatment period. However, there was no identified clinically significant effect of ADAs on pharmacodynamics, safety, or effectiveness of marstacimab.

Source: Reviewer generated table

Abbreviations: ADA, antidrug antibodies; AUC, area under the concentration-time curve; CL, clearance; C_{max} , maximum concentration; CV, coefficient of variance; IgG1, immunoglobulin G1; MRHD, maximum recommended human dose; NA, not applicable; NAb, neutralizing antibodies; PK, pharmacokinetic; SC, subcutaneous, T_{max} , time to maximum concentration; V_d , volume of distribution

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

Applicant's Proposed Dosing Regimen

The proposed dosing regimen of marstacimab is a loading dose of 300 mg by SC injection on Day 1 followed by maintenance dosage of 150 mg SC injection weekly starting on Day 8. The maintenance dosage can be adjusted to 300 mg SC injection weekly in patients weighing ≥ 50 kg when control of bleeding events is inadequate.

Selection of the Dosing Regimen for the Phase 3 Study

The Applicant's selection of the proposed dosing regimen for the Phase 3 study was based on the results of the Phase 1b/2 dose-finding study (Study B7841002). Study B7841002 was conducted in adult participants with severe hemophilia A or B with and without inhibitors for up to Day 85 (3 months). The study consisted of four marstacimab dose cohorts: (i) 300 mg SC weekly (Cohort 1; N=7), (ii) 300 mg loading dose, followed by 150 mg SC weekly (Cohort 2; N=6), (iii) 450 mg SC weekly (Cohort 3; N=6) in participants without inhibitors, and (iv) 300 mg SC weekly (Cohort 4; N=7) in participants with inhibitors. After multiple doses, the marstacimab exposure (maximum plasma concentration (C_{max}) and AUC_{tau}) increased in greater than dose-proportional manner over the range of 150 mg to 450 mg SC weekly. There was no significant difference in marstacimab pharmacokinetic between participants with or without inhibitors receiving marstacimab 300 mg weekly doses. The observed ABR up to Day 85 showed

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statistically significant reduction in all dose cohorts compared to the historic factor on-demand³ as well as pretreatment bleeding rates (mean ABR: 4.20, 1.47, 4.17, 0.72 for Cohort 1, 2, 3 and 4, respectively, while on-study; 27.6 for historic factor on-demand; and 23.0, 14.7, 20.3, 17.3 for Cohort 1, 2, 3 and 4, respectively, during pretreatment). In general, marstacimab doses of 150 mg to 450 mg weekly were well tolerated. Severe (Grade 3) treatment-related injection site reactions were reported in two participants for the 450 mg SC weekly regimen. Based on the results of the Phase 1b/2 study, while both 150 mg and 300 mg weekly doses showed significant ABR reduction and similar safety profile, a loading dose of 300 mg and maintenance dose of 150 mg weekly regimen, with the option to increase to 300 mg if needed for better bleeding control, was selected for further evaluation because of greater safety multiples and smaller injection volume.

Evaluation of the Proposed Dosing Regimen

The efficacy and safety of marstacimab loading dose of 300 mg and maintenance dose of 150 mg weekly was evaluated in the Phase 3 study (Study B7841005). Dose escalation was also available to 300 mg maintenance dose if a participant's bleeding was considered not well controlled (see subsection below regarding the evaluation of dose adjustment). For participants who received factor on-demand during the observational phase (N=33), marstacimab prophylaxis demonstrated superiority over factor on-demand as measured by ABR of treated bleeds (ABR 8.0 and 3.18 for factor on-demand and marstacimab prophylaxis, respectively). For participants who received factor prophylaxis during the observational phase (N=83), marstacimab prophylaxis demonstrated noninferiority over factor prophylaxis as measured by ABR of treated bleeds (ABR 7.85 and 5.08 for factor prophylaxis and marstacimab treatment, respectively). Refer to Section 6.2 for more details regarding the clinical efficacy of marstacimab. Refer to Section 7 for details regarding safety of marstacimab. Overall, the proposed dosing regimen seems reasonable from an efficacy and safety perspective.

Evaluation of Dosing in Adolescents

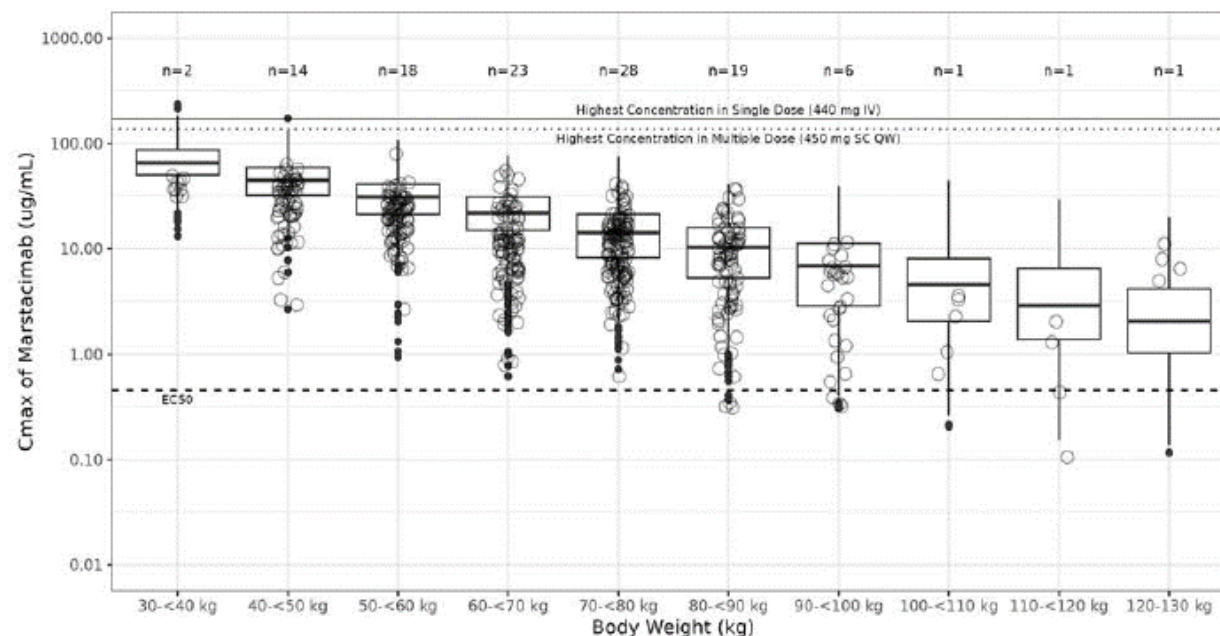
In Study B7841005, adolescents 12 years of age and older with a minimum body weight of 35 kg at the time of signing the informed consent form were also enrolled and received the same dosing regimen as adults. Marstacimab exposures were higher in adolescents compared to adults, likely due to lower body weight, as body weight is a significant covariate for marstacimab exposure (refer to Section 14.5, pharmacometrics review). However, the efficacy and safety data from both adults and adolescents in the study support the proposed dosing regimen. Furthermore, modeling and simulation using a virtual population of adults and adolescents sampled from the NHANES database demonstrated that the simulated exposure (median $C_{max,ss}$) in the lowest body weight group of 30 to 40 kg (65.2 µg/mL) were still below the highest concentration observed in participants who received marstacimab 450 mg SC weekly (QW) during clinical development (103 µg/mL in Study B7841002) without any apparent worsening of the safety profile (Figure 5). The results cover the majority of the body weight distribution for 12-year-old children

³ Per the Applicant, a historical on-demand group was constructed using patients who were on on-demand treatment in the following Pfizer studies: ReFacto AF 3082B2-4432 (B1831004), BeneFIX B1821010, and BeneFIX 3090A1-400 (B1821004). The resulting dataset were further filtered to match the key inclusion/exclusion criteria of Study B7841002 based on age and factor activity ($18 \leq \text{age} \leq 65$ and factor activity $\leq 1\%$).

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(3rd percentile weight is 29.5 kg for 12-year-old male children based on the CDC weight-for-age chart ([CDC 2001](#))). In addition, based on the 4-month safety data from the ongoing pediatric study (Study B7841008), which enrolled adolescents ≥ 12 to < 18 years of age with minimum body weight of 25 kg, no additional safety concern was observed for six participants whose body weight ranged from 33 to 61.3 kg. Therefore, the proposed dosing regimen for adolescents 12 years and older, which is same as that of the adults, is acceptable regardless of body weight.

Figure 5. Box Plot of Simulated Marstacimab $C_{\max,ss}$ (150 mg SC Weekly) for Weight Categories (Every 10 kg)



Source: Applicant's analysis, Response to FDA information request received February 29, 2024

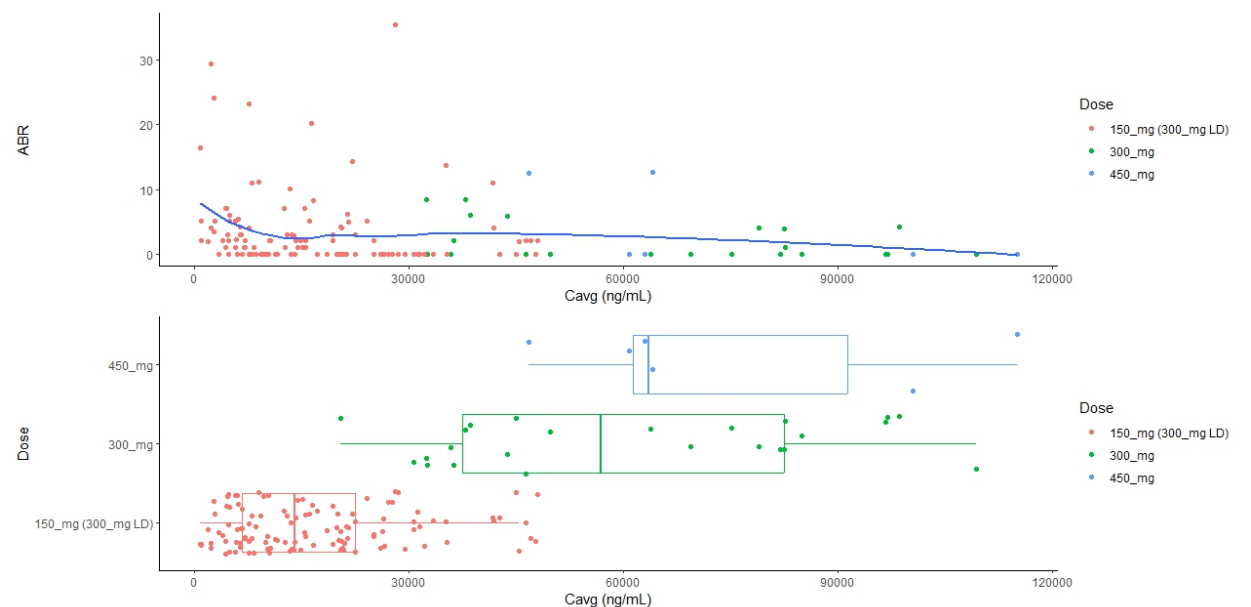
Open circles indicate observed steady-state average marstacimab concentrations. The closed circles indicate the simulated average marstacimab concentrations. EC_{50} is based on modeling of animal and Phase 1 and 2 clinical data (0.46 $\mu\text{g/mL}$). Abbreviations: $C_{\max,ss}$, maximum concentration at steady-state; EC_{50} , half-maximal effective concentration; IV, intravenous; n, number of participants; QW, once weekly; SC, subcutaneous

Evaluation of the Proposed Dose Adjustment

The Applicant proposed dose increase to marstacimab 300 mg SC weekly in participants weighing ≥ 50 kg when control of bleeding events is judged to be inadequate by the health care provider. This was implemented in the Phase 3 study (Study B7841005), once the participants were on stable treatment with marstacimab 150 mg SC weekly for at least 6 months. To evaluate whether the proposed dose adjustment is reasonable, exposure-response (E-R) analysis was conducted by FDA for the primary efficacy endpoint of ABR. The E-R analysis was conducted using LOESS nonparametric regression method with data from Phase 1b/2 study (Study B7841002), Phase 2 open-label extension study (Study B7841003), and Phase 3 study (Study B7841005) for doses 150, 300, and 450 mg. Fourteen participants who had dose escalated during the Phase 3 study were not included due to limited PK samples after dose escalation. However, the demographic and disease characteristics (i.e., age, antidrug antibody (ADA) status, hemophilia type, and body weight) of these 14 participants did not show any meaningful

differences to those included in the E-R analysis. The E-R analysis show that there is a slight trend for decrease in ABR with increase in exposure (C_{avg}) ([Figure 6](#)).

Figure 6. Exposure-Response Analysis of Marstacimab Between ABR and C_{avg}



Source: Reviewer's analysis
Abbreviations: ABR, annualized bleeding rate; C_{avg} , average plasma concentration; LD, loading dose

In addition, comparing the ABR before and after the dose adjustment shows numerical improvement in ABR for participants whose dose was increased. Among the participants who had dose increased during the study (N=14), the mean ABR decreased from 3.57 to 2.98 after dose increase in participants who received factor on-demand during the observational phase (N=3). In participants who received factor prophylaxis during the observational phase (N=11), the mean ABR decreased from 14.0 to 3.42 after dose was increased. This was also confirmed based on interim data from open-label long-term extension study, Study B7841007, which showed sustained efficacy following the dose increase to 300 mg ([Table 10](#)).

Table 10. Summary of ABR Before and After Dose Increase

Parameter	Patients Who Previously Received On-Demand Treatment (N=33)			Patients Who Previously Received Factor Prophylaxis (N=83)		
	Before Dose Increase	On or After Dose Increase	Extension Study	Before Dose Increase	On or After Dose Increase	Extension Study
N	3	3	3	11	11	10 ¹
Mean number of days	245	119	419	247	118	312
Mean ABR (Min, max)	3.57 (1.19, 8.03)	2.98 (0.00, 6.89)	1.51 (0.00, 2.71)	14.0 (2.32, 31.0)	3.42 (0.00, 11.2)	4.73 (0.00, 15.5)

Source: Reviewer's analysis
¹ One participant did not enroll in the open-label extension study.
Abbreviations: ABR, annualized bleeding rate; max, maximum; min, minimum; N, number of participants

For the body weight cutoff of 50 kg for dose escalation, the simulated exposure for different body weight groups was evaluated for both adults and adolescents ([Figure 5](#)). Based on the simulation, the median $C_{\max,ss}$ values are 65.2 and 44.6 $\mu\text{g/mL}$ for 30 to <40 kg and 40 to <50 kg, respectively, at 150 mg weekly dose, and therefore, with a 300 mg dose, the exposure will go beyond the clinical experience (highest concentration observed with 450 mg weekly dose = 103 $\mu\text{g/mL}$ in Study B7841002) in most participants weighing <50 kg, as the exposure increases greater than dose-proportionally. For participants weighing 50 kg or more, marstacimab exposures following 300 mg will stay within the clinical experience. Overall, the review team agrees with the proposed dose adjustment to marstacimab 300 mg SC weekly in participants weighing ≥ 50 kg when control of bleeding events is judged to be inadequate by the health care provider.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

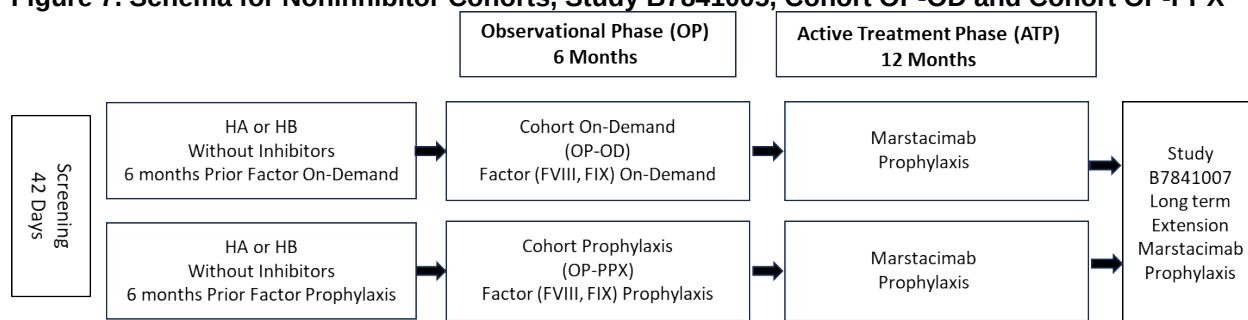
6.2.1. Study B7841005

6.2.1.1. Study Design

Study B7841005 is an open-label, multi-center, two phase (observation and active treatment) baseline-control study of marstacimab in participants aged 12 years and above with severe HA and moderately severe to severe HB with or without inhibitors. The primary efficacy objective of the study is to evaluate the effectiveness of marstacimab prophylaxis compared to factor on-demand t and separately compared to factor prophylaxis in participants with severe HA (FVIII activity <1%) or moderately severe to severe HB (FIX activity $\leq 2\%$) with or without inhibitors.

Study B7841005 enrolled participants with and without inhibitors to separate cohorts. The subject of this BLA is participants without inhibitors. Participants without inhibitors were enrolled to two independent cohorts: Cohort OP-OD (observational phase factor on-demand) enrolled participants with HA and HA without inhibitors who were receiving factor OD for at least 6 months prior to screening and Cohort OP-PPX (observational phase factor prophylaxis) enrolled participants who were receiving factor prophylaxis during 6 months prior to enrollment.

The study schema for the noninhibitor cohorts of Study B7841005 is shown in [Figure 7](#). For both Cohort OP-OD and Cohort OP-PPX, participants received factor for a 6-month OP. Participants received on demand (OD) or prophylaxis with FVIII or FIX-replacement therapy for the OP, depending on the therapy being received prior to enrollment. Upon completion of the OP, all participants entered a one-year ATP and receive marstacimab prophylaxis. All participants, regardless of therapy received during the OP, received marstacimab 300 mg SC initial loading dose followed by 150 mg SC QW. Participants who met protocol-specified dose escalation criteria based upon breakthrough bleeding, could have their dosage increased to 300 mg SC QW.

Figure 7. Schema for Noninhibitor Cohorts, Study B7841005, Cohort OP-OD and Cohort OP-PPX

Source: Clinical Reviewer figure

Cohort OP-OD: Participants who received on-demand (OD) treatment with factor replacement therapy during the observational phase (OP)

Cohort OP-PPX: Participants who received prophylaxis (PPX) treatment with factor replacement therapy during the observational phase (OP)

Abbreviations: FIX, factor IX; FVIII, factor VIII; HA, hemophilia type A; HB, hemophilia type B

The study design allows a comparison of marstacimab prophylaxis to factor OD and factor prophylaxis, where each participant serves as his/her control. Efficacy analysis compares ATP and OP, results for each cohort were independently powered and alpha controlled.

The pooling of participants with HA and HB together within the same cohort is reasonable. In the coagulation cascade, FVIII and FIX form a single enzymatic complex that goes on to activate factor X, and thus deficiency of either component (FVIII or FIX) manifests in similar coagulation deficits. The mechanism of action of marstacimab is independent of which factor is missing.

The observational period (6 months) of treatment with factor replacement (on-demand or prophylaxis) is shorter than the active treatment period (12 months) with marstacimab prophylaxis. Because the bleeding endpoints are based on the annualized bleeding rate with different durations in OP and ATP, each bleed may carry a different weight when considering the change of annual bleeding rate (ABR). A set of sensitivity analyses for evaluation of different durations and also potential seasonal effect is presented for each cohort in Section [6.2.1.5.1.1](#) and Section [6.2.1.5.2.1](#).

6.2.1.2. Eligibility Criteria

Key eligibility criteria are summarized in this section, and the full criteria are available in Section [15.1](#).

Key Eligibility Criteria

- (1) Male age 12 to <75 years inclusive with a minimum body weight of 35 kg.
- (2) Diagnosis of severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity $\leq$ 2%, respectively) documented by a clinical laboratory prior to enrollment.
- (3) Subject must also meet the following criteria:
 - (a) No detectable or documented history of inhibitors against FVIII or FIX prior to enrollment (baseline of observational phase),
 - (b) Subjects receiving routine prophylaxis 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
 - (c) Subject with on-demand [factor] treatment regimen with $\geq$ 6 acute bleeding episodes (spontaneous and/or traumatic) that required coagulation factor infusion during the 6 months period prior to screening and willing to continue to receive on-demand treatment during the observational phase. Surgical bleeding episodes do not apply to this criterion.
- (4) No known planned surgical procedure during the planned study period.
- (5) No abnormal renal or hepatic function
- (6) Patient should have platelet count $\geq$ 100,000/uL and hemoglobin level $\geq$ 10 g/dL.

It is acceptable to enroll only males in this study because hemophilia is seen almost exclusively in males. There is no basis to expect a different PK, efficacy, or safety profile in female patients, and therefore, approval should not be limited to male patients.

6.2.1.3. Study Endpoints

Primary Endpoint

The primary efficacy endpoint is the annualized bleeding rate (ABR) of treated bleeding events.

- Cohort OP-OD: The ratio of the mean ABR (marstacimab prophylaxis versus on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy.
- Cohort OP-PPX: The mean ABR difference (marstacimab prophylaxis – prior prophylactic treatment) based on adult and adolescent participants meeting the entry criteria with prior prophylaxis therapy.

In patients with hemophilia, an increased occurrence of bleeding events leads to increased morbidity and mortality, and thus, a reduction in bleeding events is clinically meaningful.

By focusing on treated bleeds, this endpoint assessed the effect of treatment on the most serious and clinically meaningful bleeding events.

Key Secondary Endpoints

- Incidence of spontaneous bleeds – spontaneous bleed is defined as bleeding for no apparent/known reason particularly into the joints, muscles, and soft tissues as opposed to traumatic bleed (i.e., bleeding event occurring for an apparent/known reason). Only treated spontaneous bleeds were counted.

Reduction in spontaneous bleeds, as opposed to bleeds that occur after trauma, is clinically meaningful to patients and prevention or reduction of spontaneous bleeds is one of the goals of modern hemophilia management.

- Incidence of joint bleeds – joint bleed is defined as a bleeding episode characterized by rapid loss of range of motion as compared with baseline that is associated with any combination of the following: pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint. Only treated joint bleeds were counted.

Repeat bleeding into a joint can be debilitating and over time result in hemophilic arthropathy. Reducing and preventing joint bleeds is beneficial to patients to help prevent the late complication of hemophilic arthropathy.

- Incidence of total bleeds (treated and untreated) – total bleeds include both treated and untreated bleeds. An untreated bleed is considered a “new untreated bleed” if occurring >48 hours after the previous new untreated bleed at the same site and occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated; an untreated bleed occurring at a different site is considered a “new untreated bleed” regardless of the time of the bleed.

Reduction of both treated and untreated bleeds is clinically meaningful to patients as any bleed impacts patients with hemophilia.

- Incidence of target joint bleeds – target joint bleed is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6-month period). To derive the “incidence” of target joint bleeds in each of the OP and ATP, “baseline” target joints were predetermined before the start of the OP. Only treated target joint bleeds were counted.

Once joint damage and inflammation occurs due to hemarthrosis, a joint can develop increased susceptibility to further bleeding, becoming a target joint. Reducing bleeds in target joints is a clinical benefit to prevent further damage and development of hemophilic arthropathy.

- Physical health domain in the Haemo-Qol (< 17 years of age) and the Hematology A Quality of Life (Haem-A-QoL) (≥17 years of age) at 6 months. The Haem-A-QoL and Haemo-Qol PROs are designed to assess health-related quality of life in patients with hemophilia. There were not enough participants < 17 years of age to analyze the PRO in adolescents. The adult version, Haem-A-QoL, consists of 46 items comprising 10 domains. There are 5 items in the physical health domain assessing painful swelling, joint pain, painful movement, difficulty walking, and needing more time to get ready. Each item is scored on a 5-point Likert scale (1 = “never”, 2 = “rarely”, 3 = “sometimes”, 4 = “often”, and 5 = “all the time”) and utilizes a recall period of the “past 4 weeks.” For reporting purposes, the individual items are combined to scales (e.g., physical health) and the scales were combined to form an overall total score ranging from 0 to 100, with lower scores indicating better physical health status.
- The Haem-A-QOL Physical Health tool has been used in a prior approval in the treatment of hemophilia and included in the United States Prescribing Information (USPI) for that product, although with a different set of items.

6.2.1.4. Statistical Analysis Plan

The statistical analysis plan (SAP) for the study was finalized on January 31, 2023, and the data cutoff date was April 17, 2023. Key information regarding statistical analysis from the clinical study report, protocol, and SAP is summarized below.

Analysis Population

The following analyses sets were defined for the statistical analysis.

- (1) Entered analysis set: All participants who sign the informed consent document.
- (2) Enrolled analysis set: All entered participants assigned to a treatment in OP.
- (3) All safety analysis set: For participants with prior prophylaxis in OP, all participants who received at least 1 prophylaxis or on-demand treatment at OP; for participants with on-demand in OP, all participants who completed any of the procedures for Visit 2 (OP baseline). Participants who changed from a noninhibitor to an inhibitor on or before ATP Day -7 testing were excluded from this population.

- (4) Marstacimab safety analysis set: All participants who were administered at least one dose of marstacimab during the ATP.
- (5) Modified intent-to-treat (mITT) analysis set: All participants who completed OP and received at least one dose of marstacimab in ATP (excluding participants with inhibitors who were treated with factor prophylaxis in the OP). Participants who changed from a noninhibitor to inhibitor on or before ATP Day -7 testing were excluded from mITT. This population was utilized for all efficacy analyses.

In this review, the population used for the primary analysis (defined as mITT above) is referred to as the efficacy analysis set, and included participants who had both OP and ATP data. Because the primary analyses were based on the comparison between OP and ATP, the efficacy analysis set could not be based on all participants with OP data. With only less than 10% of participants who did not have ATP data, the impact of efficacy analysis was minimum.

Sample Size Determination

For adequate powering, the Applicant planned a sample size of 25 participants when marstacimab prophylaxis was compared with on-demand treatment to demonstrate superiority and 60 participants when marstacimab prophylaxis was compared with factor prophylaxis for noninferiority.

These sample sizes 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 12.5 for factor on-demand. The mean bleeds over 6 months for factor prophylaxis was initially assumed as 2.5 with an added scenario of 2.35 that was obtained as the weighted average of hemophilia A and B ABRs based on the meta-analysis; the weights were based on the prevalence of each hemophilia type. The mean bleeds over 12 months for marstacimab prophylaxis was initially assumed as 4 with two 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 two 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 participant; 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 $6 \cdot \mu_i$ where μ represented the mean bleeding for marstacimab prophylaxis for complete follow up. [Table 11](#) below demonstrated that the planned sample sizes maintain adequate power (>90%) for all scenarios except for the most pessimistic case.

Table 11. Power From Simulations With Different Follow-Up

Testing/Sample Size	Assumed Marstacimab Mean Bleeding for 12 Months ¹	Assumed Reference Mean Bleeding for 6 Months ²	Simulated Power ³ (%)
Superiority vs. on-demand factor with N=25	4 3.46 2.67	12.5	98.9 >99 >99
Noninferiority vs. factor prophylaxis with N=60	4 3.46 2.67 4 3.46 2.67	2.5 2.35	90.1 96.9 >99 86.9 95.4 >99

Source: Study B7841005 SAP v6 dated January 31, 2023, Table 3.

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 hemophilia 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 participant; 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 $6 \cdot \mu_i$.

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants; vs., versus

Analysis of the Primary Endpoint

The primary efficacy endpoint was the ABR of treated bleeding events, which was derived for each participant using the following formula: $ABR = \text{number of bleeds requiring treatments} / (\text{days on treatment period} / 365.25)$. If a participant did not complete a treatment period, the days on treatment ended at the last dosing date+6 days.

Superiority Versus Factor-Based On-Demand Treatment

A repeated measure negative binomial regression model via generalized estimating equation approach was used with log link function. In the model, the number of bleeds was a response variable, and treatment (marstacimab prophylaxis or factor-based on-demand) was a factor. The time on treatment in log years was an offset variable to account for different duration on treatment. The working correlation was set as unstructured. The superiority criterion of marstacimab prophylaxis over factor-based on-demand is if the 2-sided 95% confidence interval (CI) for the mean ABR ratio (marstacimab prophylaxis/factor-based on-demand) was below the preset threshold of 0.5.

The Applicant proposed the superiority criterion for comparison versus on-demand factor treatment for the primary and key secondary endpoints related to bleeding to be 0.5 in the SAP. The review team considered a threshold of 0.5 acceptable because it is more conservative than a commonly accepted criterion of 1.

Noninferiority Versus Factor Prophylaxis

A repeated measure negative binomial regression model via generalized estimating equation approach was used with identity link function. In the model, the number of bleeds was a response variable, and duration (in years) and the interaction by treatment (marstacimab prophylaxis or

factor prophylaxis) and duration were factors. The working correlation was set as unstructured. Treatment difference in the mean ABRs was obtained using a contrast within the interaction term. The noninferiority criterion of marstacimab prophylaxis over factor prophylaxis was if the upper bound of the 2-sided 95% CI for the mean ABR difference (marstacimab prophylaxis – factor prophylaxis) lies below the preset noninferiority (NI) margin 2.5 for primary endpoint. The review team considered this NI margin acceptable. Refer to Section [16.1](#) regarding the Applicant’s derivation of the NI margin 2.5 for the primary endpoint.

Subgroup Analysis for the Primary Endpoint

Results for the primary endpoint ABR of treated bleeds, when compared with on-demand and factor prophylaxis treatment for participants without inhibitors, were summarized by hemophilia types, age, race, ethnicity, and geographic region, respectively.

Sensitivity/Supplementary Analysis for the Primary Endpoint

Sensitivity/supplementary analyses of the ABR of treated bleeds were conducted to support the conclusion of the primary analysis with robustness under different handlings of intercurrent events (preventative infusion, dose increase, treatment discontinuation, or potentially missing records) and potential concerns for bias (due to carryover effect or seasonal effect) from the primary analysis.

Impact of Seasonal and Carryover Effects

There was no washout period in the one-way cross-over design of Study B7841005 and the comparison between the 6-month OP and 12-month ATP resulted in potential seasonal effect on the primary endpoint.

The Applicant conducted the following sensitivity analyses for the primary endpoint (ABR for treated bleeds).

- (1) The main analysis was repeated with the same model for the primary analysis by comparing 6-month OP versus excluding the first month of marstacimab treatment during the ATP.
- (2) The main analysis was repeated with the same model for the primary analysis by comparing 6-month OP versus data only matched the calendar days in ATP.
- (3) The bleed rates were compared descriptively during the early part of the treatment period (Months 1 to 6 in ATP) and the latter part of the treatment period (Months 7 to 12 ATP).

The review team conducted additional sensitivity analyses by comparing the 6-month OP with the second half ATP to evaluate the robustness of the primary analysis results.

Handling of Intercurrent Events for the Primary Endpoint

The Applicant performed additional supplementary analyses using the same model for the primary endpoint with following approaches to dealing with intercurrent events and discontinuation.

- (1) To assess the impact of preventative treatment for medical/dental procedures, sport activity or physical therapy (plus 72 hours): include bleeding during preventative infusion.
- (2) To assess the impact of dose increase, the main analysis was repeated with the same model, using the following approaches:
 - (a) Including data after dose increase.
 - (b) Imputing the portion after dose increase using the mean ABR calculated 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 mean ABR calculated based on bleeds 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.

Although the Applicant considered dose increase as an intercurrent event, because dose increase was allowed per protocol, the Division did not agree, and sensitivity and tipping point analyses for dose increase are thus not included with the review. An evaluation of the proposed dose adjustment (i.e., increase) is included in Section [6.1](#).

Analysis of the Key Secondary Endpoints

The first four key secondary endpoints of incidence of (1) spontaneous bleeds, (2) joint bleeds, (3) total bleeds either treated or untreated, and (4) target joint bleeds were similarly derived as the derivation of the ABR of treated bleeds and were analyzed using the same negative binomial model as that for the primary endpoint.

The estimand for the bleeding-related key secondary endpoints had the same attributes of treatment, population, intercurrent events, and population-level summary as in the primary estimand. The Applicant did not conduct sensitivity or supplemental analysis for the bleeding-related key secondary endpoints.

Another key secondary endpoint was change from baseline in physical health domain in the Haem-A-QoL at 6 months. For reporting purposes, the individual 5 items in the Haem-A-QoL

HYMPAVZI (marstacimab-hncq) injection

were combined to domain scales (e.g., physical health) and the domain scales were combined to form an overall total score. The transformed scale score (TSS) on a scale of 0 to 100 was calculated using the following formula and used for the analyses.

Equation 1. Transformed Scale Score Calculation

$$\text{TSS} = 100 \times \frac{\text{raw score} - \text{minimal possible raw score}}{\text{maximum possible raw score} - \text{minimum possible raw score}}$$

Source: Study B7841005 SAP v6 dated January 31, 2023

Abbreviations: SAP, statistical analysis plan; TSS, transformed scale score

Each TSS reflects the average response of the valid items when there were at least a minimum required number of valid items. Otherwise, the TSS is set as missing. To compute the TSS for the physical health domain, a minimum of three out of five valid items is required.

The Wilcoxon signed rank test was used to perform the superiority and/or noninferiority comparison. Missing observations were handled via multiple imputation approach under missing at random assumption. Sensitivity tipping point analyses would also be conducted via successively applying pessimistic assumptions for missingness due to withdrawals because of adverse event (AE) or lack of efficacy.

Hierarchical Testing Sequence and Multiple Testing Strategy

The ordering of statistical testing for Study B7841005, Cohort OP-OD and Cohort OP-PPX proposed in the SAP is shown in [Table 12](#) (column SAP). During the course of the review, the Applicant clarified that they were seeking to establish substantial evidence of effectiveness based on two independent and completed cohorts conducted under a single protocol, B7841005. The Agency agreed with the characterization of the two cohorts as the equivalent of independent substudies, allowing them to be analyzed separately. As a result, individual alphas with 0.05 could be given to each cohort separately. The new hierarchical sequences based on independent analysis of the OP-OD and OP-PPX cohorts, which is the sequence used for this review, is shown in [Table 12](#) (column review).

As seen in the table, the testing of superiority over factor prophylaxis in the OP-PPX cohort was not dependent on the results of noninferiority testing of physical health domain in Haem-A-QoL in the OP-PPX. If noninferiority versus factor prophylaxis was established for all bleeding endpoints, testing for superiority versus factor prophylaxis may be conducted using the same statistical model in a way to control the Type I error rate.

Table 12. Ordering of Statistical Testing, Study B7841005

Endpoint	Cohort OP-OD		Cohort OP-PPX			
	Superiority vs. OD		Noninferiority vs. PPX		Superiority vs. PPX	
	SAP ¹	Review ²	SAP ¹	Review ²	SAP ¹	Review ²
Treated bleeds (primary)	1	1	2	1	12	6
Incidence of spontaneous bleeds	3	2	7	2	15	9
Incidence of joint bleeds	4	3	8	3	16	10
Incidence of target joint bleeds	6	5	10	5	18	12
Incidence of total bleeds	5	4	9	4	17	11

Endpoint	Cohort OP-OD		Cohort OP-PPX			
	Superiority vs. OD		Noninferiority vs. PPX		Superiority vs. PPX	
	SAP ¹	Review ²	SAP ¹	Review ²	SAP ¹	Review ²
Physical health domain in Haem-A-QoL questionnaire at 6 months	11	6	13	7	14	8

Source: FDA table, updated based on Study B7841005 SAP v6 dated January 31, 2023, Table 6

¹ Testing order for study as specified in the SAP.

² Testing order by Cohort used by Agency for review.

Abbreviations: Haem-A-QoL, Hematology A Quality of Life; OD, on-demand; OP, observational phase; PPX, prophylaxis; SAP, statistical analysis plan; vs., versus

[Table 13](#) summarizes the decisions rules for primary and key secondary endpoints.

Table 13. Endpoints and Decision Rules

Endpoint		Superiority vs. OD (Cohort OP-OD)	Noninferiority vs. PPX (Cohort OP-PPX)	Superiority vs. PPX (Cohort OP-PPX)
Primary	Treated bleeds	ABR ratio <0.5	ABR difference 2.5	ABR difference <0
	Incidence of spontaneous bleeds	ABR ratio <0.5	ABR difference 2.5	ABR difference <0
	Incidence of joint bleeds		ABR difference 2.5	
Secondary	Incidence of total bleeds		ABR difference 2.9	
	Incidence of target joint bleeds		ABR difference 1.2	
	Physical health domain in Haem-A-QoL at 6 months	Median difference <0	Median difference: 10 units	Median difference <0

Source: FDA table, updated based on Study B7841005 SAP v6 dated January 31, 2023, Table 4

Abbreviations: ABR, annualized bleeding rate; OD, on-demand; OP, observational phase; PPX, prophylaxis; QoL, quality of life; SAP, statistical analysis plan

The results of the analysis for cohort OP-OD superiority over factor on-demand r and for cohort OP-PPX noninferiority versus factor prophylaxis are presented separately in Section [6.2.1.5.1.1](#) and Section [6.2.1.5.2.1](#). Because the analysis of cohort OP-PPX superiority over factor prophylaxis was not used in the Agency's final determination for evidence of efficacy, it is only briefly described in Section [6.2.1.5.2.2](#), with additional details included in Section [16.4](#) for completeness.

6.2.1.5. Results of Analyses

Data Quality and Integrity

Data were provided electronically in standard format with a study data tabulation model and analysis data model. Statistical analysis software programs used to create key efficacy and safety outputs for the study were submitted along with the data of the BLA. The Applicant also provided a clear definition file for datasets and detailed analysis programs for assisting reviews.

6.2.1.5.1. On-Demand Factor Therapy During Observation Period, Cohort OP-OD

Patient Disposition

A total of 37 participants with prior on-demand treatment using factor replacement entered the study. A total of 34 (91.9%) participants completed the 6-month OP. Three participants discontinued during the OP, two of them due to protocol deviation and one due to relocation. Among the 34 participants who completed the OP, 33 entered the 12-month ATP, which composed the efficacy analysis set for Cohort OP-OD. No participants discontinued during the ATP.

Table 14. Patients Disposition by Phase, Study B7841005, Cohort OP-OD

Parameter	N (%)
<i>Observational phase (OP)</i>	
Participants entered	37 (100)
Discontinued	3 (8.1)
Reason for discontinuation	
Protocol deviation	2 (5.4)
No longer meets eligibility criteria	0
Other	1 (2.7)
Completed	34 (91.9)
Completed but not entered ATP	1 (2.7)
<i>Active treatment phase (ATP)</i>	
Participants entered	33 (100)
Discontinued	0
Reason for discontinuation	
Adverse event	0
Withdrawal by subject	0
Completed	33 (100)
Plan to participate in the extension study (B7841007)	32 (97)

Source: ds.xpt and adsl.xpt; Software: R

Duration is 6 months in observational phase.

Abbreviations: ATP, active treatment phase; N, number of participants; OD, on-demand; OP, observational phase

Demographics and Baseline Clinical Characteristics

[Table 15](#) and [Table 16](#) summarize demographics and disease characteristics of participants in Cohort OP-OD at baseline. In Cohort OP-OD, there were no meaningful differences in baseline demographics and disease characteristics between participants who entered the OP (n=37) and those who entered the ATP (n=33), despite the discontinuation of four participants (three with HA and one with HB) prior to the ATP (did not receive treatment with marstacimab).

Table 15. Baseline Demographic Characteristics, Study B7841005, Cohort OP-OD

Parameter	Entered OP (N=37)	Entered ATP (N=33)
Age (years), n (%)		
Mean (SD)	31.4 (10.5)	31.9 (11.04)
Median (min, max)	29 (15, 58)	29 (15, 58)
12 to <18	2 (5.4)	2 (6.1)
18 to 44	31 (83.8)	27 (81.8)
45 to 64	4 (10.8)	4 (12.1)
Sex, n (%)		
Male	37 (100)	33 (100)
Race, n (%)		
Asian	24 (64.9)	22 (66.7)
White	13 (35.1)	11 (33.3)
Ethnicity, n (%)		
Hispanic or Latino	4 (10.8)	3 (9.1)
Not Hispanic or Latino	33 (89.2)	30 (90.9)
Geographical region, n (%)		
Asia	23 (62.2)	21 (63.6)
Europe	8 (21.6)	7 (21.2)
Middle East	2 (5.4)	2 (6.1)
North America (Canada, Mexico, U.S.)	4 (10.8)	3 (9.1)
Region group of participation, n (%)		
Non-U.S.	37 (100)	33 (100)
U.S.	0	0
Baseline eGFR ¹ (mL/min/1.73 m ²), n (%)		
≥90	32 (86.5)	29 (87.9)
≥60 to <90	5 (13.5)	4 (12.1)
Weight (kg), n	37	33
Mean (SD)	70.2 (19.4)	68.2 (19.10)
Median (min, max)	71 (43.2, 114)	70 (43.2)
Height (cm), n	37	33
Mean (SD)	171.5 (8.8)	170.8 (8.52)
Median (min, max)	170 (157.2, 190)	170 (157.2, 189)
Body mass index (kg/m ²), n	37	33
Mean (SD)	23.7 (5.61)	23.2 (5.57)
Median (min, max)	24.4 (15.3, 38.8)	24 (15.3, 38.8)

Source: adsl.xpt; Software: R

¹ Estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) method for adult participants; eGFR using [Schwartz et al. \(2009\)](#) method for adolescent participants.

Abbreviations: ATP, active treatment phase; eGFR, estimated glomerular filtration rate; max, maximum; min, minimum; N, number of participants in treatment group; n, number of participants with given characteristic; OD, on-demand; OP, observational phase; SD, standard deviation; U.S., United States

Table 16. Baseline Disease Characteristics, Study B7841005, Cohort OP-OD

Parameter	Entered OP (N=37)	Entered ATP (N=33)
Hemophilia type, n (%)		
Hemophilia A	29 (78.4)	26 (78.8)
Hemophilia B	8 (21.6)	7 (21.2)
Age groups (years), n (%)		
Adolescents (ages 12 to <18)	2 (5.4)	2 (6.1)
Adults (ages 18 to <75)	35 (94.6)	31 (93.9)

Parameter	Entered OP (N=37)	Entered ATP (N=33)
Age and hemophilia type, n (%)		
Adolescents, hemophilia A	2 (5.4)	2 (6.1)
Adolescents, hemophilia B	0	0
Adults, hemophilia A	27 (73)	24 (72.7)
Adults, hemophilia B	8 (21.6)	7 (21.2)
ISTH disease severity, n (%)		
Moderate severity	1 (2.7)	0
Severe	36 (93.3)	33 (100)
Number of target joints at baseline ¹ , n (%)		
0	1 (2.7)	0
1	8 (21.6)	7 (21.2)
2	16 (43.2)	14 (42.4)
≥3	12 (32.4)	12 (36.4)

Source: adsl.xpt; Software: R

¹ Target joints are defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period).

Abbreviations: ATP, active treatment phase; ISTH, International Society on Thrombosis and Hemostasis; N, number of participants in treatment group; n, number of participants with given characteristic; OD, on-demand; OP, observational phase

6.2.1.5.1.1. Superiority of Marstacimab (ATP) Over On-Demand Factor (OP)

Efficacy Results of the Primary Endpoint

In Study B7841005, the primary efficacy endpoint was ABR of treated bleeds. The model based ABR was 3.18 for marstacimab prophylaxis during the ATP and 38.00 for on-demand factor during the OP. The ABR ratio is 0.084 (95% CI: 0.059, 0.119) with the p-value<0.0001, showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5, thus meeting the predetermined superiority criterion for marstacimab over on-demand factor. These results are summarized in [Table 17](#).

Table 17. Results of the Primary Endpoint (ABR of Treated Bleeds), Study B7841005, Cohort OP-OD

Parameter	On-Demand Factor (OP) (N=33)	Marstacimab Prophylaxis(ATP) (N=33)
ABR, model-based (95% CI)	38.00 (31.03, 46.54)	3.18 (2.09, 4.85)
ABR ratio vs. OD (95% CI), p-value	0.084 (0.059, 0.119), <0.0001	

Source: Study B7841005 Interim Clinical Study Report, Table 9; FDA-verified.

Results were based on negative binomial regression model (see Section 6.2.1.4 for details).

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OD, on-demand; OP, observational phase; vs., versus

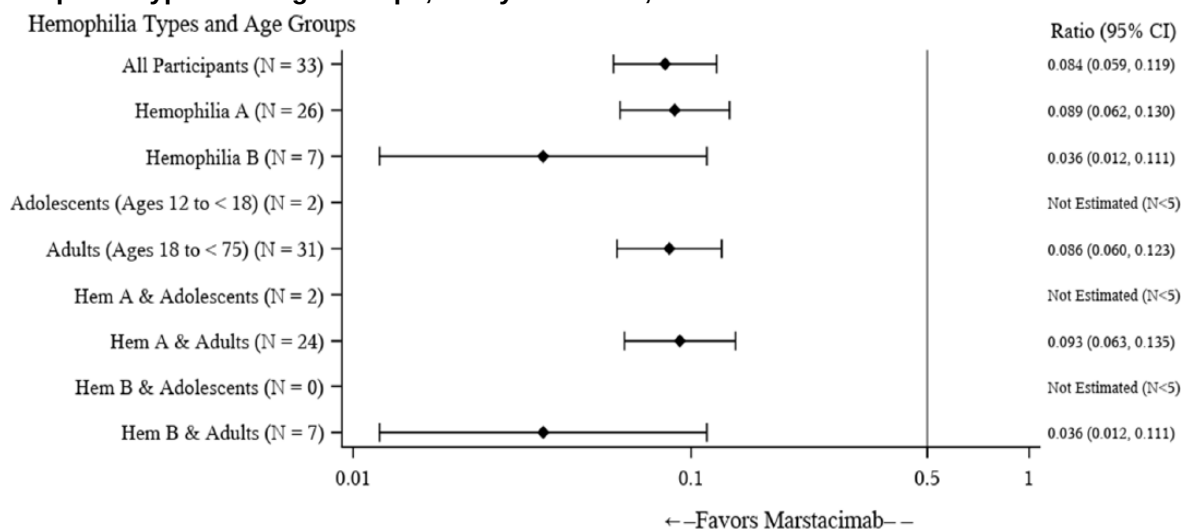
Subgroup Analyses Results of the Primary Endpoint

[Figure 8](#) shows the subgroup analysis results for the primary endpoint by age and hemophilia type. The model based mean ABR for subgroups with sample sizes less than five were not estimated. Overall, the treatment effect of marstacimab prophylaxis compared to on-demand factor was consistent by hemophilia type and age groups. Of note, HB subgroup had a wide

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confidence interval with sample size N=7, although it showed similar direction compared with the overall group and the HA subgroup. Since the sample sizes within these subgroups were small and the study was not originally powered to draw statistical conclusions for these subgroups, the results should be interpreted with caution.

Figure 8. Subgroup Analyses: Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Hemophilia Types and Age Groups, Study B7841005, Cohort OP-OD



Source: Study B7841005 Interim Clinical Study Report, Figure 2; FDA-verified.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, number of participants in treatment group; OD, on-demand; OP, observational phase

At the request of the Agency, the Applicant conducted additional analyses based on further refined age groups (ages 12 to <18, ages 18 to <35, and ages 35 to <75). The age of 35 represented the median age of the adult population across the groups of on-demand factor and factor prophylaxis during the OP. The results showed a consistent pattern across different subgroups (i.e., age, race, ethnicity, and geographic region). Refer to Section [16.2](#) for more information.

Subgroup analysis was not conducted for different countries as the 33 participants in the OP-OD cohort were enrolled at over 9 countries, making subgroups too small to yield meaningful analysis. Note that there were no U.S. participants in the on-demand factor cohort.

Sensitivity/Supplementary Analyses Results of the Primary Endpoint

To ensure the robustness of the primary analysis results, the following sensitivity/supplementary analyses were conducted.

Sensitivity Analysis Results for Evaluation of Carry-Over and Seasonal Effects

The sensitivity analysis results for evaluation of carry-over and seasonal effects for Cohort OP-OD are shown in [Table 18](#).

The study did not include a washout period between the OP with factor and initiation of the ATP with marstacimab. To account for possible carry-over effect, the Applicant compared the ABR rate for the 6-month OP and the ABR rate for the ATP, excluding the first month of treatment with marstacimab. As seen in [Table 18](#), the ABR ratio of marstacimab versus OD using the full ATP period was 0.084 (95% CI: 0.059, 0.119) compared to 0.082 (95% CI: 0.057, 0.118) when the first month of ATP is excluded. These similar estimated ABR ratios versus OD demonstrated there was no carry-over effect from the treatment with factor during the OP to treatment with marstacimab during ATP.

To compare the potential impact of seasonality, the Applicant compared the 6-month OP ABR with an ATP ABR based on the matched calendar days and with an ATP ABR based on the second 6-month period of the ATP. While similar, the matched calendar days and second half ATP are not the same for participants whose treatment duration are not exact 180 days during OP and 365 days during ATP. For both comparisons, as seen in the table, the ATP ABR for a subset of the ATP period is lower than the ATP ABR for the entire ATP period. This results in smaller ratios versus OD. For the calendar matched ATP, the ratio OD is 0.062 (95% CI: 0.043, 0.090) and for the second half ATP, the ratio versus OD is 0.063 (95% CI: 0.041, 0.098) compared to the ratio OD based on the entire ATP of 0.084 (95% CI: 0.059, 0.119). This suggests there may be some seasonality; however, the CIs are overlapping and thus no conclusion can be drawn. Most importantly, the upper bound of the 95% CIs for the ABR ratios for both the full ATP and the calendar matched ATP were less than 0.5, the predetermined superiority criterion for superiority, and thus the sensitivity analysis results supported that the superiority criterion versus on-demand factor for the primary endpoint was met.

The Applicant also conducted analyses for the primary endpoint based on the first and second halves of ATP ([Table 19](#)) for completed participants who remained on a dose of 150 mg marstacimab SC QW. The mean ATP ABR based on the first 6 months of the ATP (3.99 [SD =2]) is larger than the ATP ABR based on the second 6 months of the ATP (2.42 [SD =3.024]); however, the medians are nearly identical (2.0 for the first 6 months compared to 2.01 for the second 6 months). This suggests the higher ABR during the first 6 months is due to an extreme value, which is confirmed where the max ABR for the first 6 months was 35.93 compared to 10.15 during the second 6 months.

Overall, the Division concludes that neither lack of washout period nor seasonality changed the conclusion that superiority versus on-demand factor is met for marstacimab prophylaxis.

Table 18. Sensitivity Analyses of the Primary Endpoint (ABR of Treated Bleeds) for Carry-Over and Seasonal Effect, Study B7841005, Cohort OP-OD

Parameter	On-Demand Factor (OP)	Marstacimab Prophylaxis (ATP)
N	33	33
ABR, model-based (95% CI)	38.00 (31.03, 46.54)	3.18 (2.09, 4.85)
Ratio vs. OD (95% CI)	0.084 (0.059, 0.11)	
<i>Excluding first month ATP</i>		
N	33	33
ABR, model-based (95% CI)	37.96 (31.00, 46.49)	3.11 (2.02, 4.77)
Ratio vs. OD (95% CI)	0.082 (0.057, 0.118)	
<i>Matched calendar days in ATP</i>		
N	33	33
ABR, model-based (95% CI)	38.04 (31.07, 46.57)	2.36 (1.58, 3.51)
Ratio vs. OD (95% CI)	0.062 (0.043, 0.090)	
<i>Second half (6 months) ATP</i>		
N	33	30
ABR, model-based (95% CI)	38.02 (31.07, 46.53)	2.40 (1.54, 3.75)
Ratio vs. OD (95% CI)	0.063 (0.041, 0.098)	

Source: FDA table updated based on Study B7841005 Interim Clinical Study Report, Table 10.

Results were based on negative binomial regression model (see Section 6.2.1.4 for details).

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OD, on-demand; OP, observational phase; vs., versus

Table 19. Descriptive Summary of the ABR for Treated Bleeds for the First and Second Half of ATP, Study B7841005, Cohort OP-OD

ABR Descriptive Summary	First Half of ATP	Second Half of ATP
N	30	30
Mean	3.99	2.42
SD	7.168	3.024
Median	2.00	2.01
Q1, Q3	0.00, 5.99	0.00, 4.15
Min, max	0.00, 35.93	0.00, 10.15

Source: Study B7841005 Interim Clinical Study Report, Table 11; FDA-verified

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; max, maximum; min, minimum; N, number of participants in treatment group; OD, on-demand; OP, observational phase; Q1, first quartile; Q3, third quartile; SD, standard deviation

Supplementary Analysis Results for Handling of Intercurrent Events

Intercurrent events included preventative infusion and treatment discontinuation or potentially missing bleeding records.

- *Preventative infusion.* By including bleeding during preventative infusion, the model based ABR ratio was 0.083 (95% CI: 0.058, 0.118), similar to results of the primary analysis.
- *Treatment discontinuation or potentially missing bleeding records.* There was one participant who had a dosing gap (≥ 35 days), during which time no bleed was reported. When data during dose gap was imputed using the mean ABR, the model based ABR ratio was 0.082 (95% CI: 0.058, 0.117), similar to results of the primary analysis.
- The tipping point analysis assumed the bleed rate during the dose gap (≥ 35 days) as multiples of successively larger (>1) factors of the ABRs during the observed portions. The results

demonstrated that unless the tipping multiplier was 154 or higher, the conclusion regarding superiority over on-demand is robust.

The above supplementary analyses results confirmed the robustness of the Applicant's final efficacy analysis results for data of marstacimab prophylaxis superiority comparison with factor on-demand. Refer to Section [16.3](#) for a summary table of the supplementary analyses results.

Efficacy Results of Key Secondary Endpoints

Because the primary efficacy endpoint analysis was statistically significant, the key secondary efficacy endpoints for comparison versus on-demand factor were tested in the prespecified hierarchical order, given any previous endpoint showed statistical significance:

- Incidence of spontaneous bleeds
- Incidence of joint bleeds
- Incidence of total bleeds (treated and untreated)
- Incidence of target joint bleeds
- Physical health domain in Haem-A-QoL at 6 months

[Table 20](#) summarizes the analysis results for all major key secondary efficacy endpoint for the OP-OD cohort. All analyses were confirmed by FDA.

Table 20. Results of the Key Secondary Endpoints, Study B7841005, Cohort OP-OD

Endpoints in Order of Testing Hierarchy		On-Demand Factor (OP) (N=33)	Marstacimab Prophylaxis (ATP) (N=33)
Spontaneous bleeds	ABR, model-based (95% CI)	30.93 (24.12, 39.67)	2.44 (1.61, 3.69)
	Ratio vs. OD (95% CI)	0.079 (0.054, 0.114)	
	p-value	<0.0001	
Joint bleeds	ABR, model-based (95% CI)	32.86 (26.15, 41.29)	2.83 (1.81, 4.44)
	Ratio vs. OD (95% CI)	0.086 (0.059, 0.125)	
	p-value	<0.0001	
Total bleeds	ABR, model-based (95% CI)	47.76 (39.60, 57.60)	7.39 (5.08, 10.74)
	Ratio vs. OD (95% CI)	0.155 (0.116, 0.207)	
	p-value	<0.0001	
Target joint bleeds	ABR, model-based (95% CI)	23.18 (17.20, 31.24)	1.84 (1.06, 3.17)
	Ratio vs. OD (95% CI)	0.079 (0.051, 0.124)	
	p-value	<0.0001	
Physical health domain in Haem-A-QoL at 6 months	Median estimate (95% CI)	-1.12 (-12.19, 9.95)	-12.35 (-19.60, -5.11)
	Estimated difference (95% CI)	-10.678 (-24.001, 2.645)	
	p-value	0.1161	

Source: Study B7841005 Interim Clinical Study Report, Tables 13 to 16 and 19; FDA-verified

The sample size for ABR endpoints was N=33 for both OP and ATP phases, the sample size for PRO endpoint (physical health domain in Haem-A-QoL at 6 months) was N=31.

Results for the ABR endpoints were based on negative binomial regression model (see Section [6.2.1.4](#) for details). For the PRO endpoint, results were based on the Wilcoxon signed rank test and exact confidence interval using Walsh averages.

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OD, on-demand; OP, observational phase; PRO, patient-reported outcome; QoL, quality of life; vs., versus

Spontaneous Bleeds

The model based ABR was 2.44 for marstacimab during the ATP, and 30.93 for on-demand factor during the OP. The ABR ratio was 0.079 (95% CI: 0.054, 0.114) with the p-value<0.0001, showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5 and achieved the predetermined superiority criterion for marstacimab over on-demand factor.

Joint Bleeds

The model based ABR was 2.83 for marstacimab during the ATP, and 32.86 for on-demand factor during the OP. The ABR ratio was 0.086 (95% CI: 0.059, 0.125) with the p-value<0.0001, showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5 and achieved the predetermined superiority criterion for marstacimab over on-demand factor.

Total Bleeds

The model based ABR was 7.39 for marstacimab during the ATP, and 47.76 for on-demand factor during the OP. The ABR ratio was 0.155 (95% CI: 0.116, 0.207) with the p-value<0.0001, showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5 and achieved the predetermined superiority criterion for marstacimab over on-demand factor.

Target Joint Bleeds

The model based ABR was 1.84 for marstacimab during the ATP, and 23.18 for on-demand factor during the OP. The ABR ratio was 0.079 (95% CI: 0.051, 0.124) with the p-value<0.0001, showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5 and achieved the predetermined superiority criterion for marstacimab over on-demand factor.

Physical Health Domain in Haem-A-QoL at 6 Months

The model based median score change from baseline in physical health domain in the Haem-A-QoL at 6 months was -12.35 for marstacimab during the ATP, and -1.12 for factor on-demand during the OP. The estimated difference was -10.678 (95% CI: -24.001, 2.645) with the p-value=0.1161. A negative difference indicates an improvement in quality of life related to physical health. However, the estimated difference of -10.678 was associated with 95% CI that crossed 0, with a p-value=0.1161, and thus is not considered statistically significant.

For the Haemo-QoL (adolescents 12 to 17 years) physical health domain score, there were not enough participants (N=2) for any formal statistical analysis. The analyses of change from baseline in physical health domain in Haem-A-QoL (adults ≥ 17 years) at 6 months was based on 31 out of 33 participants.

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No participant discontinued the study due to lack of efficacy or adverse event; thus, the tipping point analysis of change from baseline at 6 months in physical health domain of the Haem-A-QoL for on-demand treatment at OP was not performed.

At the request of the Agency, the Applicant conducted nonparametric analyses for the primary and key secondary endpoints related to ABR to assess the robustness of the primary analysis results. Their results based on the nonparametric approach (i.e., Wilcoxon signed rank test) for the ABR differences (ATP - OP) showed $p\text{-value} < 0.0001$ for all major efficacy endpoints related to ABR. The review team confirmed these results and therefore concluded that the primary analysis results for on-demand superiority comparisons are positive with statistical significance.

6.2.1.5.2. Prophylaxis Factor Therapy During Observation Period, Cohort OP-PPX

Patient Disposition

A total of 91 participants with prior treatment with factor prophylaxis entered the study. Of those, a total of 84 (92.3%) participants completed the 6-month OP. Seven participants discontinued during the OP, 2 of them due to protocol deviation and 5 due to no longer meeting the eligibility criteria. Among the 84 participants who completed the OP, 83 entered the 12-month ATP treatment with marstacimab. These 83 participants composed the efficacy analysis set for Cohort OP-PPX. During the ATP, five participants discontinued marstacimab, 4 of them withdrew and 1 discontinued due to an AE.

Table 21. Patients Disposition by Phase, Study B7841005, Cohort OP-PPX

Parameter	N (%)
Observational phase (OP)	
Participants entered	91 (100)
Discontinued	7 (7.7)
Reason for discontinuation	
Protocol deviation	2 (2.2)
No longer meets eligibility criteria	5 (5.5)
Other	0
Completed	84 (92.3)
Completed but not entered ATP	1 (1.1)
Active treatment phase (ATP)	
Participants entered	83 (100)
Discontinued	5 (4.8)
Reason for discontinuation	
Adverse event	1 (1.2)
Withdrawal by participant	4 (4.8)
Completed	78 (94)
Plan to participate in the extension study (B7841007)	76 (91.6)

Source: ds.xpt and adsl.xpt; Software: R

Duration is 6 months of observational phase.

Abbreviations: ATP, active treatment phase; N, number of participants in treatment group; OP, observational phase; PPX, prophylaxis

Demographics and Baseline Clinical Characteristics

[Table 22](#) and [Table 23](#) summarizes demographic and disease characteristics of participants in Cohort OP-PPX. There were no significant differences between OP and ATP despite eight participants (seven with HA and one with HB) discontinuing the study prior to ATP.

Table 22. Baseline Demographics Characteristics, Study B7841005, Cohort OP-PPX

Parameter	Entered OP (N=91)	Entered ATP (N=83)
Age (years), n (%)		
Mean (SD)	33 (14.7)	32.6 (14.81)
Median (min, max)	31 (13, 66)	31 (13, 66)
12 to <18	18 (19.8)	17 (20.5)
18 to 44	47 (51.6)	43 (51.8)
45 to 64	25 (27.5)	22 (26.5)
65 to 74	1 (1.1)	1 (1.2)
Sex, n (%)		
Male	91 (100)	83 (100)
Race, n (%)		
Black or African American	1 (1.1)	1 (1.2)
Asian	37 (40.7)	36 (43.4)
White	52 (57.1)	45 (54.2)
Not reported	1 (1.1)	1 (1.2)
Ethnicity, n (%)		
Hispanic or Latino	9 (9.9)	9 (10.8)
Not Hispanic or Latino	82 (90.1)	74 (89.2)
Baseline eGFR ¹ (mL/min/1.73 m ²), n (%)		
≥90	68 (74.7)	62 (74.7)
≥60 to <90	19 (20.9)	19 (22.9)
≥30 to <60	1 (1.1)	0
Missing	3 (3.3)	2 (2.4)
Weight (kg) n	91	83
Mean (SD)	70.1 (15.1)	69.1 (15.32)
Median (min, max)	70.4 (35, 120)	69 (35, 120)
Height (cm) n	91	83
Mean (SD)	170.7 (8.3)	170.5 (8.43)
Median (min, max)	170.7 (141, 185)	170.7 (141, 185)
Body mass index (kg/m ²) n	91	83
Mean (SD)	23.9 (4.22)	23.6 (4.25)
Median	24 (15.2, 36)	27.7 (15.2, 36)
Geographical region, n (%)		
Asia	31 (34.1)	30 (36.1)
Europe	39 (42.9)	32 (38.6)
Middle East	10 (11.0)	10 (12)
North America	11 (12.1)	11 (13.3)

Source: adsl.xpt; Software: R

¹ Estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease (MDRD) method for adult participants; eGFR using [Schwartz et al. \(2009\)](#) method for adolescent participants.

Abbreviations: ATP, active treatment phase; eGFR, estimated glomerular filtration rate; max, maximum; MDRD, Modification of Diet in Renal Disease; min, minimum; N, number of participants in treatment group; n, number of participants with given characteristic; OP, observational phase; SD, standard deviation

Table 23. Baseline Disease Characteristics, Study B7841005, Cohort OP-PPX

Parameter	Entered OP (N=91)	Entered ATP (N=83)
Hemophilia type, n (%)		
Hemophilia A	72 (79.1)	65 (78.3)
Hemophilia B	19 (20.9)	18 (21.7)
Age groups (years), n (%)		
Adolescents (ages 12 to <18)	18 (19.8)	17 (20.5)
Adults (ages 18 to <75)	73 (80.2)	66 (79.5)
Age category and hemophilia type, n (%)		
Adolescents hemophilia A	13 (14.3)	13 (15.7)
Adolescents hemophilia B	5 (5.5)	4 (4.8)
Adults hemophilia A	59 (64.8)	52 (62.7)
Adults hemophilia B	14 (15.4)	14 (16.9)
ISTH disease severity, n (%)		
Moderate severity	0	0
Severe	91 (100)	83 (100)
Number of target joints at baseline, ¹ n (%)		
0	38 (41.8)	36 (43.4)
1	21 (23.1)	19 (22.9)
2	15 (16.5)	15 (18.1)
≥3	17 (18.7)	13 (15.7)

Source: adsl.xpt; Software: R

¹ Target joints are defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period).

Abbreviations: ATP, active treatment phase; ISTH, International Society on Thrombosis and Hemostasis; N, number of participants in treatment group; n, number of participants with given characteristic; OP, observational phase

6.2.1.5.2.1. Noninferiority of Marstacimab (ATP) Over Prophylaxis With Factor (OP)

Efficacy Results of the Primary Endpoint

In Study B7841005, the primary efficacy endpoint was ABR of treated bleeds. The model based ABR was 5.08 for marstacimab during the ATP and 7.85 for prophylaxis with factor during the OP. The ABR difference was -2.77 (95% CI: -5.37, -0.16). The upper bound of the 95% CI for the ABR difference was less than the prespecified noninferiority margin of 2.5, thus meeting the predetermined noninferiority criterion of marstacimab over prophylaxis with factor. These results are summarized in [Table 24](#). The review team also evaluated the assay sensitivity (i.e., the factor prophylaxis during the OP's performance) to ensure that NI results are interpretable. Detailed examination is shown in Section [16.4](#).

Table 24. Results of the Primary Endpoint (ABR of Treated Bleeds), Study B7841005, Cohort OP-PPX

Parameter	Factor Prophylaxis (OP) (N=83)	Marstacimab Prophylaxis (ATP) (N=83)
ABR, model-based (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Difference vs. factor prophylaxis (95% CI)	-2.77 (-5.37, -0.16)	

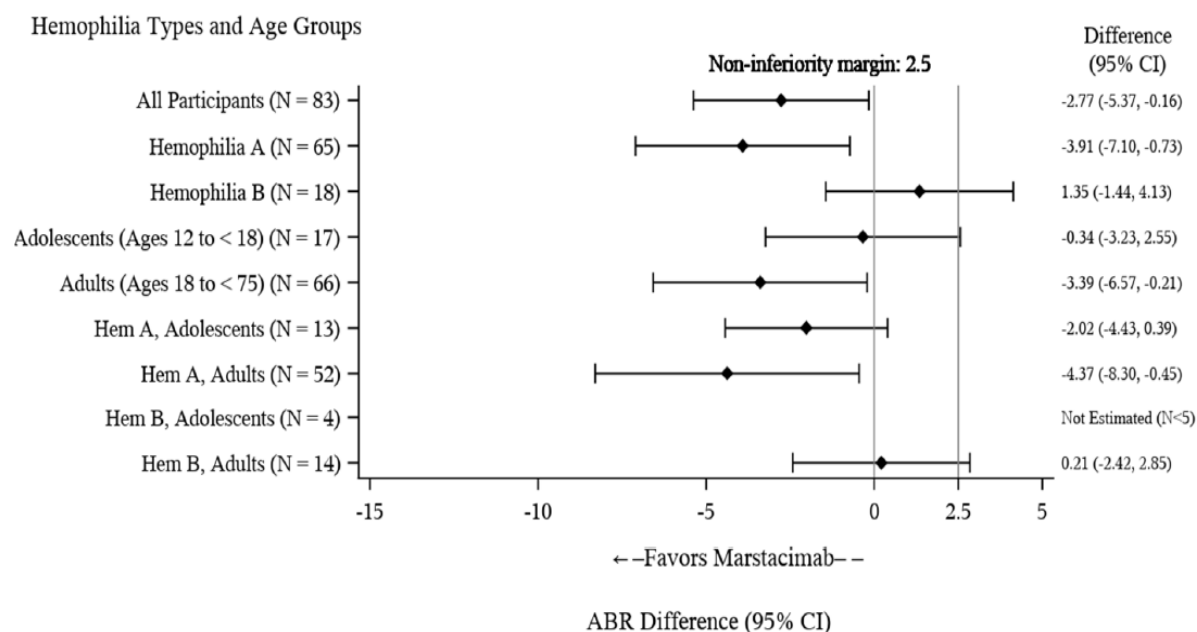
Source: Study B7841005 Interim Clinical Study Report, Table 24; FDA-verified

The prespecified noninferiority criterion (upper bound of the 95% CI for the difference) was 2.5 for treated bleeds. Results were based on negative binomial regression model (see Section 6.2.1.4 for details).

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OP, observational phase; vs., versus

Subgroup Analyses Results of the Primary Endpoint

The subgroup analysis results for the primary endpoint by age and hemophilia type are shown in Figure 9. The model based mean ABR for subgroup of adolescents in the HB subgroup with sample size less than five was not estimated. The upper bound of the CI for the ABR difference among HB participants (N=18), HB adults (N=14), and adolescent participants (N=17) exceeded the noninferiority margin 2.5, while the upper bound of the CI for the ABR difference among HA participants did not. This issue is discussed further as a key efficacy issue in Section 6.3.1.

Figure 9. Subgroup Analyses: Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Hemophilia Types and Age Groups, Study B7841005, Cohort OP-PPX

Source: Study B7841005 Interim Clinical Study Report, Figure 7; FDA-verified

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; hem, hemophilia; N, number of participants in treatment group; OP, observational phase

At the request of the Agency, the Applicant conducted additional analyses based on refined age groups (ages 12 to <18, ages 18 to <35, and ages 35 to <75) created by adding age of 35 years, which represented the median age of the adult population across the groups of on-demand factor

and factor prophylaxis at the OP, to bracket around. In general, the results showed consistent pattern across subgroups by age, race, ethnicity, and geographic region except those for the subgroups: age (ages 12 to <18, N=17) had model based ABR difference -0.34 and 95% CI (-3.23, 2.55) and North America (N=11) had model based ABR difference 0.43 and 95% CI (-2.43, 3.29), where the upper bound of the 95% CI exceeded the noninferiority margin 2.5. This was possibly due to small sample sizes within those subgroups without adequate study power to detect differences within subgroups. Refer to Section [16.2](#) for more information. Of note, there was only one participant with age greater than 65.

Subgroup analysis was not conducted for different countries as the 83 participants in the PPX cohort were enrolled at 14 countries, making subgroups too small to yield meaningful analysis.

Note that there was only one participant enrolled at a U.S. site.

Sensitivity/Supplementary Analyses of the Primary Endpoint

To ensure the robustness of the primary analysis results, the Applicant conducted the following sensitivity/supplementary analyses.

Sensitivity Analysis for Evaluation of Carry-Over and Seasonal Effects

The sensitivity analysis results for evaluation of carry-over and seasonal effects for Cohort OP-OD are shown in [Table 25](#). The study did not include a washout period between the OP with factor prophylaxis and initiation of the ATP with marstacimab prophylaxis. To account for possible carry-over effect, the Applicant compared the ABR rate for the 6-month OP and the ABR rate for the ATP, excluding the first month of treatment with marstacimab. As seen in [Table 25](#), the difference versus factor prophylaxis using the full ATP period is -2.77 (95% CI: -5.37, -0.16) compared to -2.56 (95% CI: -5.26, 0.13) when the first month of ATP is excluded. The similarity in difference versus factor prophylaxis with and without the first month of ATP demonstrated there was no carry-over effect from the treatment with factor prophylaxis during the OP to marstacimab prophylaxis during ATP.

To compare the potential impact of seasonality, the Applicant compared the 6-month OP ABR with an ATP ABR based on the matched calendar days and with an ATP ABR based on the second 6-month period of the ATP. While similar, the matched calendar days and second half ATP are not the same for participants whose treatment duration are not exactly 180 days during OP and 365 days during ATP. For both comparisons, as seen in the table, the ATP ABR for a subset of the full ATP is lower than the ATP ABR for the entire ATP period. This results in smaller differences versus factor prophylaxis. For the matched calendar days ATP, the difference versus factor prophylaxis is -4.40 (95% CI: -7.10, -1.70) and for the second half ATP, the difference versus factor prophylaxis is -4.92 (95% CI: -7.69, -2.14) compared to -2.77 (95% CI: -5.37, -0.16) for the full ATP.

This suggests there may be some seasonality; however, the CIs are overlapping and thus no conclusion can be drawn. Importantly, the upper bound of the 95% CIs for the ABR difference for both comparisons were less than the noninferiority margin 2.5. Thus, the sensitivity analysis results supported that primary analysis that the noninferiority criterion versus factor prophylaxis cohort for the primary endpoint was met.

HYMPAVZI (marstacimab-hncq) injection

The Applicant also conducted analyses for the primary endpoint (ABR of treated bleeds) of the first and second half of ATP ([Table 26](#)) for completed participants who remained on a dose of 150 mg marstacimab SC QW, comparing factor prophylaxis during the OP and marstacimab prophylaxis during the ATP. Although the mean ABR of participants was lower in the second half of ATP compared with that in the first half of ATP (2.82 versus 3.54, respectively), the median ABR during the first and second half of ATP were similar. This supports that there is no concern in terms of seasonal effect.

Overall, the Division concludes that neither lack of washout period nor seasonality changed the conclusion that noninferiority versus factor prophylaxis is met for marstacimab prophylaxis.

Table 25. Sensitivity Analyses of the Primary Endpoint (ABR of Treated Bleeds) for Carryover and Seasonal Effects, Study B7841005, Cohort OP-PPX

Parameter	Factor Prophylaxis (OP) (N=83)	Marstacimab Prophylaxis (ATP) (N=83)
N	83	83
ABR, model-based (95% CI)	7.85 (5.09, 10.61)	5.08 (3.40, 6.77)
Difference vs. factor prophylaxis (95% CI)	-2.77 (-5.37, -0.16)	
<i>Excluding first month ATP</i>		
N	83	82
ABR, model-based (95% CI)	7.82 (5.06, 10.58)	5.26 (3.44, 7.08)
Difference vs. factor prophylaxis (95% CI)	-2.56 (-5.26, 0.13)	
<i>Matched calendar days in ATP</i>		
N	83	79
ABR, model-based (95% CI)	7.88 (5.12, 10.63)	3.47 (2.07, 4.87)
Difference vs. factor prophylaxis (95% CI)	-4.40 (-7.10, -1.70)	
<i>Second half (6 months) ATP</i>		
N	83	67
ABR, model-based (95% CI)	7.88 (5.12, 10.63)	2.96 (1.54, 4.38)
Difference vs. factor prophylaxis (95% CI)	-4.92 (-7.69, -2.14)	

Source: FDA table, updated based on Study B7841005 Interim Clinical Study Report, Table 25

Results were based on negative binomial regression model (see Section 6.2.1.4 for details).

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OP, observational phase; PPX, prophylaxis; vs., versus

Table 26. Descriptive Summary of the ABR for Treated Bleeds for the First and Second Half of ATP, Study B7841005, Cohort OP-PPX

ABR Descriptive Summary	First Half of ATP	Second Half of ATP
N	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

Source: Study B7841005 Interim Clinical Study Report, Table 26; FDA's analysis

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; max, maximum; min, minimum; N, number of participants in treatment group; OP, observational phase; PPX, prophylaxis; Q1, first quartile; Q3, third quartile; SD, standard deviation

Thus, the results for the primary endpoint (ABR of treated bleeds) for noninferiority versus factor prophylaxis were determined to be robust, and do not appear to be affected by any carry-over and seasonal effects.

Supplementary Analysis for Handling of Intercurrent Events

Intercurrent events included preventative infusion and treatment discontinuation or potentially missing bleeding records.

- *Preventative infusion:* By including bleeding during preventative infusion, the model based ABR difference was -2.82 (95% CI: -5.43, -0.20) and compatible with results of the primary analysis.
- *Treatment discontinuation or potentially missing bleeding records:* There were six participants with ATP discontinuation or dosing gap (≥ 35 days) during which time no bleed was reported. When data after treatment discontinuation was imputed using the mean ABR from prior to discontinuation and data during a dosing gap was imputed using the mean ABR from before and after the dosing gap, the model based ABR difference was -3.12 (95% CI: -5.73, -0.51). The tipping point analysis assumed the bleed rate after study discontinuation or during the dose gap (≥ 35 days) as multiples of successively larger (>1) factors of the ABRs during the observed portions. The results demonstrated that unless the tipping multiplier was 4.6 or higher, the conclusion regarding noninferiority over factor prophylaxis is the same. A tipping multiplier of 4.6 is considered high, and therefore, we conclude the results are robust.

Refer to Section [16.3](#) for a summary table of the supplementary analyses results.

Efficacy Results of Key Secondary Endpoints

Since the upper bound of the 95% CI for the ABR difference for the primary endpoint was less than the prespecified noninferiority margin 2.5 and met the noninferiority criterion of marstacimab prophylaxis compared with factor prophylaxis, the following key secondary efficacy endpoints for comparison versus factor prophylaxis were tested in the prespecified hierarchical order:

- Incidence of spontaneous bleeds
- Incidence of joint bleeds
- Incidence of total bleeds (treated and untreated)
- Incidence of target joint bleeds
- Physical health domain in Haem-A-QoL at 6 months

The efficacy results for the key secondary endpoints are summarized in [Table 27](#).

Table 27. Results of the Key Secondary Endpoints, Study B7841005, Cohort OP-PPX

Endpoints in Testing Hierarchy	Estimates	Factor Prophylaxis (OP) (N=83)	Marstacimab Prophylaxis (ATP) (N=83)
Spontaneous bleeds	ABR, model-based (95% CI)	5.86 (3.54, 8.19)	3.78 (2.25, 5.31)
	Difference vs. factor prophylaxis (95% CI)	-2.087 (-4.232, 0.060)	

Endpoints in Testing Hierarchy	Estimates	Factor Prophylaxis (OP) (N=83)	Marstacimab Prophylaxis (ATP) (N=83)
Joint bleeds	ABR, model-based (95% CI)	5.66 (3.33, 7.98)	4.13 (2.59, 5.67)
	Difference vs. factor prophylaxis (95% CI)	-1.527 (-3.698, 0.644)	
Total bleeds	ABR, model-based (95% CI)	8.84 (5.97, 11.72)	5.97 (4.13, 7.81)
	Difference vs. factor prophylaxis (95% CI)	-2.868 (-5.613, -0.122)	
Target joint bleeds	ABR, model-based (95% CI)	3.36 (1.59, 5.14)	2.51 (1.25, 3.76)
	Difference vs. factor prophylaxis (95% CI)	-0.856 (-2.413, 0.701)	
Physical health domain in Haem-A-QoL at 6 months	Not tested due to rules of hierarchical testing. Estimated median difference: -2.2 (95% CI: -9.1, 4.6)		

Source: Study B7841005 Interim Clinical Study Report, Tables 28 to 31; FDA-verified.

The prespecified noninferiority criterion (upper bound of the 95% CI for the difference) was 2.5 for spontaneous bleeds, joint bleeds; 1.2 for target joint bleeds; 2.9 for total bleeds. Results were based on negative binomial regression model (see Section 6.2.1.4 for details).

Abbreviations: ABR, annualized bleeding rate; ATP, active treatment phase; CI, confidence interval; N, number of participants in treatment group; OP, observational phase; QoL, quality of life; vs., versus

Spontaneous Bleeds

The model based ABR was 3.78 for marstacimab during the ATP and 5.86 for prophylaxis with factor during the OP. The ABR difference was -2.087 (95% CI: -4.232, 0.060). The upper bound of the 95% CI for the ABR difference was less than the prespecified noninferiority margin 2.5 and achieved the noninferiority criterion of marstacimab over prophylaxis with factor.

Joint Bleeds

The model based ABR was 4.13 for marstacimab prophylaxis during the ATP and 5.66 for prophylaxis with factors during the OP. The ABR difference was -1.527 (95% CI: -3.698, 0.644). The upper bound of the 95% CI for the ABR difference was less than the prespecified noninferiority margin 2.5 and achieved the noninferiority criterion of marstacimab over prophylaxis with factor.

Total Bleeds

The model based ABR was 5.97 for marstacimab prophylaxis during the ATP, and 8.84 for factor prophylaxis during the OP. The ABR difference was -2.868 (95% CI: -5.613, -0.122). The upper bound of the 95% CI for the ABR difference was less than the prespecified noninferiority margin 2.9 and achieved the noninferiority criterion of marstacimab over prophylaxis with factor.

Target Joint Bleeds

The model based ABR was 2.51 for marstacimab prophylaxis during the ATP, and 3.36 for prophylaxis with factor during the OP. The ABR difference was -0.856 (95% CI: -2.413, 0.701). The upper bound of the 95% CI for the ABR difference was less than the prespecified noninferiority margin 1.2 and achieved the noninferiority criterion of marstacimab over factor prophylaxis.

Thus, the noninferiority criteria were met for all key secondary endpoints related to ABR.

Physical Health Domain in Haem-A-QoL at 6 Months

The change from baseline at 6 months in physical health domain in Haem-A-QoL could not be tested due to the hierarchical testing rules (see [Table 13](#)) as the superiority for the primary endpoint (treated bleeds) versus factor prophylaxis was not robust using different parametric and nonparametric methods and thus could not be established (See Section [16.4](#)). The estimated median difference was -2.2 (95% CI: -9.1, 4.6).

6.2.1.5.2.2. Superiority of Marstacimab (ATP) Over Prophylaxis With Factor (OP)

Although the primary endpoint for superiority over prophylaxis with factor for the OP-PPX cohort could be tested based on the hierarchical testing sequence that considered the two cohorts independently, the results were not found to be robust. Demonstration of superiority was not necessary for the Agency's ultimate regulatory decision, and the Applicant did not seek a claim of superiority over factor prophylaxis in the proposed USPI.

For completeness, detailed analysis of superiority over factor prophylaxis are presented in Section [16.4](#).

6.2.1.5.3. Additional Assessments, Cohorts OP-OD and OP-PPX

Impact of Financial Compensation at One Site

During the BLA review, the review team noted that participants from OMAN site 1091 received financial compensation. Among the five participants in site 1091, there was one participant enrolled to the OP-OD cohort and four participants enrolled to the OP-PPX. For both superiority versus the OP-OD cohort and noninferiority versus OP-PPX, the review team conducted additional sensitivity analyses by different imputation methods (replacing the ABR value by 0, mean, and median of the remaining participants' ABRs), the results remained statistically significant and supported the primary analysis results.

Applicability of Results to the U.S. Population

Only one participant from the United States was enrolled in Study B7841005 Cohort OP-PPX and no participants from the United States in Cohort OP-OD. Overall, there were 15 participants enrolled in the North America region (6 participants from Canada, 8 participants from Mexico, and one participant from the United States). The Applicant attributed low enrollment in the United States mainly to early shutdown during the COVID-19 pandemic and later resumption of enrollment in the United States compared to other regions. The Applicant asserts that the results from Study B7841005 are applicable to the U.S. population given the well-known etiology of HA and HB, similarity of treatment paradigm of hemophilia globally, and similarity between the population enrolled to Study B7841005 population and to the U.S. hemophilia population with respect to demographic, disease severity, available therapies, and response to treatment. A

subgroup analysis based on geographic regions of the efficacy of marstacimab prophylaxis found the ABRs were numerically lower in North America (2.57) and the Middle East (2.98), followed by Europe (4.52), and numerically higher in Asia (7.55).

The clinical team concurs with the Applicant's justification that hemophilia is primarily a congenital disease caused by deficiency in coagulation factor VIII or IX. The current standard treatment based on factor replacement (on-demand or prophylaxis) is consistent across global regions. The World Federation of Hemophilia guidelines for the management of hemophilia do not adjust the guidelines based on geographical location. The high-level subgroup analysis of ABR based on region does not demonstrate a higher ABR in North America which would suggest possible lower efficacy. Therefore, the review team concludes that the results of Study B7841005 are applicable to the U.S. population.

6.2.1.6. Conclusions of Benefit

In Cohort OP-OD analysis of superiority of marstacimab over factor on-demand, the model based ABR ratio for the primary endpoint (treated bleeds) was 0.084 (95% CI: 0.059, 0.119) with the p -value <0.0001 , showing a statistically significant test result. The upper bound of the 95% CI for the ABR ratio was less than 0.5, the preselected superiority criterion. The model based ABR ratios for the first four key secondary endpoints spontaneous bleeds, joint bleeds, total bleeds, and target joint bleeds were 0.079 (95% CI: 0.054, 0.114), 0.086 (95% CI: 0.059, 0.125), 0.155 (95% CI: 0.116, 0.207), 0.079 (95% CI: 0.051, 0.124), with the p -value <0.0001 , respectively. Thus, the superiority criteria of marstacimab over factor on-demand for major efficacy endpoints related to ABR were achieved.

In Cohort OP-PPX analysis for noninferiority of marstacimab over factor prophylaxis, the model based ABR difference for the treated bleeds was -2.77 (95% CI: -5.37, -0.16) with upper bound of the 95% CI less than the prespecified noninferiority margin 2.5. The model based ABR differences for the key secondary endpoints spontaneous bleeds, joint bleeds, total bleeds, and target joint bleeds were 2.087 (-95% CI: 4.232, 0.060), -1.527 (95% CI: -3.698, 0.644), -2.868 (95% CI: -5.613, -0.122), -0.856 (95% CI: -2.413, 0.701), respectively. The upper bounds of the CIs for the difference were less than the prespecified noninferiority margins, which were 2.5 for spontaneous bleeds, joint bleeds; 1.2 for target joint bleeds; 2.9 for total bleeds. Thus, the noninferiority criteria of marstacimab over factor prophylaxis for all major efficacy endpoints related to ABR were achieved. The sensitivity and supplemental analyses demonstrated that the final results for the primary efficacy endpoints were robust.

Patients with HA without factors and HB without factors have limited treatment options for the prevention (prophylaxis) and treatment (on-demand or episodic) of bleeds. Greater number of bleeding events leads to increased morbidity and mortality. Marstacimab is a first-in-class human monoclonal antibody that neutralizes TFPI activity and enhances coagulation.

Prophylactic treatment that prevents or reduces bleeding, especially joint bleeds and intracerebral hemorrhage, is important for long-term outcomes, in particular prevention of joint arthropathy, in patients with hemophilia. Factor prophylaxis has risks which include the need for recurrent venous access, and the frequency of infusions can be burdensome to patients. Additionally, there is a risk for the development of inhibitors with factor replacement. Marstacimab provides for a

nonfactor prophylaxis option with a subcutaneous weekly dosing regimen for patients with hemophilia A and B without inhibitors, decreasing treatment burden and eliminating the risk of developing inhibitors to factor. Additionally, marstacimab prophylaxis is superior to on-demand factor therapy for patients who are not on a prophylaxis regimen.

6.3. Key Efficacy Review Issues

6.3.1. The ATP ABR Point Estimates and 95 % CI in Hemophilia B Compared to Hemophilia A in Cohort OP-PPX

Issue

Observed smaller ABR difference between ATP ABR and OD ABR in participants with HB compared to HB for Cohort OP-PPX

Background

As seen in [Figure 9](#), in the OP-PPX cohort, the mean ABR difference in participants with HA (N=65) is -3.91 (95% CI: -7.10, -7.73) and in participants with HB (N=18) is 1.35 (95% CI: -1.44, 4.13). Thus, the mean ABR difference and upper bound of the 95% CI in participants with HA are below the noninferiority margin. However, in participants with HB, while the mean ABR difference is below the noninferiority margin, the upper bound of the 95% CI is above the margin.

Assessment

In response to the Agency's requests for additional information regarding the observed lower point estimate for the ABR difference for the HB subgroup compared to the HA subgroup, the Applicant provided the following possible explanation:

- The observation could be due to four participants in the HB subgroup with unexpectedly high ABRs during the ATP (ABR >10). These four participants comprise two adolescents and two adults. Both adolescents and one adult dose escalated to 300 mg SC QW during the ATP. All four participants continued into the long-term extension Study B7841007. In looking at this further, the higher mean ABR for participants with HB during the ATP was driven primarily by two participants with ABR of 16.1 (b) (6) and 19.5 (b) (6). Both participants

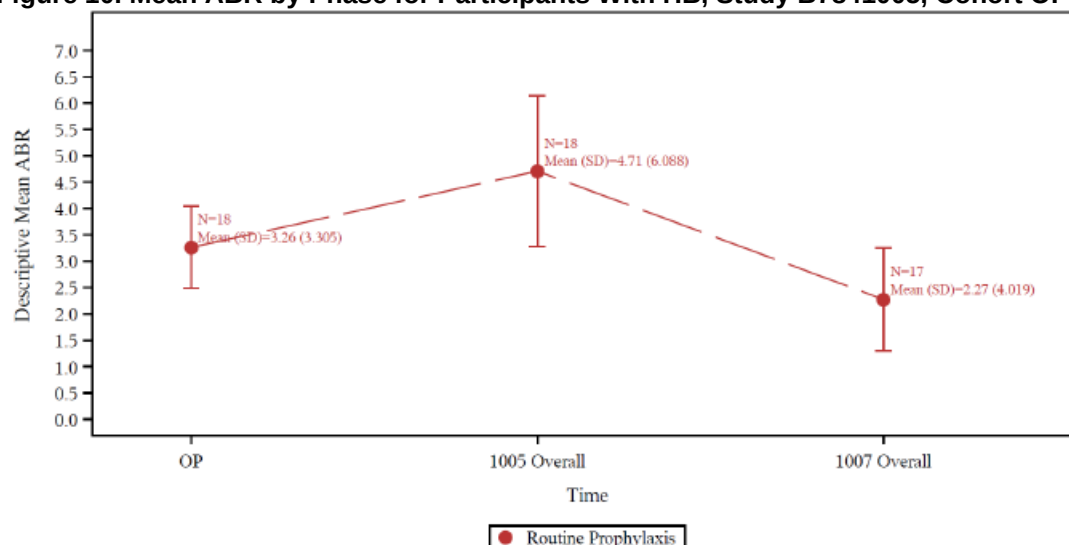
HYMPAVZI (marstacimab-hncq) injection

received dose escalation to 300 mg QW late in ATP at Day 204 (b) (6) and Day 300 (b) (6).

- Participant (b) (6) is an adult who had an ABR of 16.1 while on marstacimab 150 mg SC QW (204 days) compared to 4.68 while on 300 mg SC QW (156 days) during the ATP, with an overall ABR including both the 150 mg and 300 mg doses of 11.2. Of note, the ABR during the OD on factor prophylaxis was 0.
- Participant (b) (6) is an adolescent who, per the Applicant, had a marked increase in physical activity during the ATP, leading to traumatic joint bleeds (14/18 of his bleeding episodes during the ATP). The ABR for participant (b) (6) while on 150 mg SC QW (300 days) was 19.5 compared to 10.2 while on 300 mg SC QW (72 days). His overall ABR, including both the 150 mg and 300 mg doses, was 17. His ABR decreased to 7.38 after 99 days during the open-label extension period. Of note, his ABR during the OD on factor prophylaxis was 5.8.

Figure 10 shows the mean ABR for participants with HB for the OP, ATP, and during the open-label-extension (OLE), Study B7841007. As seen in the figure, the mean ABR was higher in the ATP compared to the OP; however, during the OLE, the ABR decreased to less than the ABR during the OP. The mean (SD) ABR for participants with HB in Cohort-OP-PPX was 3.26 (3.3) during the OP compared to 4.71 (6.08) during ATP and 2.27 (4.02) in Study B7841007.

Figure 10. Mean ABR by Phase for Participants With HB, Study B7841005, Cohort OP-PPX



Source: Applicant's Response to FDA IR Figure 23a_2_2

Abbreviations: ABR, annualized bleeding rate; HB, hemophilia B; N, number of patients in treatment group; OP, observational phase; SD, standard deviation

In addition to looking at those participants with HB with ABRs during the ATP >10, the review team looked at those participants who had a significantly higher ABR during ATP compared to during OD. There were three participants with HB who had at least five more bleeds (annualized) in the ATP compared to the OP (annualize). Participants (b) (6) are discussed above. Participant (b) (6) is 13-year-old who had 0 bleeds reported during the OD and an ABR of 11 during the ATP. All bleeds were categorized as traumatic and occurred

between Study Days 54 and 314. Six of the bleeds involved joints and five involved soft tissue or muscle, at varying sites. Compliance with marstacimab was 100%. The Applicant stated that in follow up by the Applicant with the principal investigator, the participant was noted to have become more active during the ATP.

Conclusion

The review team concludes that despite some observed differences in point estimate of the ABR difference in participants with HA compared to HB, marstacimab prophylaxis demonstrates efficacy in both populations. The information provided by the Applicant for specific participants with HB who had extreme ABRs during the ATP provided plausible reasons why these individuals may have had higher bleeds during ATP when receiving marstacimab compared to during OP when receiving factor prophylaxis. Two participants with poor bleed control on 150 mg marstacimab prophylaxis during the ATP compared to factor prophylaxis during the OP appeared to have markedly improved ABR when the marstacimab dose was increased to 300 mg. One additional participant with HB who had a much higher ABR during ATP than OP was noted as being more active during ATP, potentially contributing to the higher point estimate observed in participants with HB.

Given the overall small sample size of the OP-PPX cohort, subgroups by hemophilia type were small and the study was not powered to draw statistical conclusions on subgroups. For both HA and HB, the point estimate of the ABR difference did not exceed the prespecified noninferiority margin. While the 95% CI for the mean ABR difference for the subgroup of participants with HB was above the noninferiority margin, we note that this margin was selected for use with the entire OP-PPX cohort (HA and HB). Reassurance of the efficacy of marstacimab in participants with HB is further provided by the observation in the OP-OD cohort where the ATP ABR was significantly reduced compared to the OP ABR (ABR =23.49 (95% CI: 19.28, 28.63) versus ATP ABR of 0.86 (95% CI: 0.26, 2.8)). Based on mechanism of action of marstacimab, which is independent of which factor is deficiency (FVIII for HA or FIX for HB), one would not expect a difference in effect between HA and HB. Overall, the review team concludes there is a treatment effect of marstacimab prophylaxis in participants with HA and in participants with HB.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Marstacimab binds to human TFPI, specifically at an epitope on the Kunitz-type serine protease inhibitor K2 domain (K2), with affinity in the low- to sub-nanomolar range (Section [13.1](#)) but does not bind the K1 or K3 domains of TFPI. Marstacimab showed similar binding affinity to the combined K1K2 domains (via the K2 domain) of TFPI from human, cynomolgus monkey, rabbit, mouse, and the Wistar Han rat.

Toxicology studies of 3 months duration that utilized high doses of marstacimab in healthy rats (up to 1,000 mg/kg/week, representing >200-times the clinical exposure at the maximum

recommended weekly human dose (MRHD) and in healthy monkeys (up to 500 mg/kg/week, representing >200-times the clinical exposure at the MRHD, based on the AUC) caused an increase in D-dimer and increased the incidence of microscopic emboli in the lung and injection site, but no significantly adverse thrombi were identified by histopathology. A low incidence of acute minimal lung emboli was observed sporadically at the end of the 6-month rat study at 60 (1F, 1M), 180 (4F, 2M) and 1000 mg/kg (1F, 0M) (versus 0F and 0M with the vehicle control), and across other studies ([Table 75](#)). These emboli were of uncertain clinical significance because they (a) lacked a clear dose-response relationship, (b) were observed in the absence of adverse secondary lesions in the lungs (i.e., there was no evidence of any lesions significant enough to damage lung tissues or impact lung function), (c) occurred without any evidence of altered prothrombin time, and (d) were not observed in all studies. This suggests that the pharmacodynamic effect in healthy animals is nearly completely muted, presumably due to intact coagulatory hemostatic regulatory mechanisms. Despite the absence of a clear dose-response relationship between marstacimab and lung emboli in healthy animals, a hypothetical risk of clotting (e.g., lung or other emboli) in hemophilia patients given marstacimab cannot be excluded.

A fertility and early embryofetal developmental (FEED) study was conducted in marstacimab treated males mated with treatment naïve females. The study identified no adverse effects at 1000 mg/kg/week (i.e., the no observed adverse effect level (NOAEL), which represented exposure >200-times the clinical exposure at the MRHD). Based on results of the FEED study, there is no evidence that marstacimab poses a risk to male fertility or the health of the resulting embryo to the time of implantation. Marstacimab was not tested in reproduction studies in female animals because hemophilia A and B occur almost exclusively in males. In the absence of such data, the use of effective contraceptive measures by female patients with hemophilia should be considered during treatment with marstacimab, and for five half-lives after the last dose.

In summary, despite the absence of a robust signal for emboli in healthy animals treated with marstacimab, the hypothetical risk of emboli in patients with hemophilia cannot be excluded. No adverse impact on male fertility or (male-mediated effect on) early embryonic development was demonstrated.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Although healthy animals in toxicology studies did not identify any risk, based on marstacimab mode of action, the risk of emboli in hemophilia patients cannot be ruled out. [Section 7.6.3](#) discusses thromboembolic events during clinical studies and the risk of thromboembolic events is included in Warnings and Precautions of the USPI based on class labeling.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Marstacimab is not currently approved or marketed in the United States or in any country.

7.4. FDA Approach to the Safety Review

The safety assessment for the intended population of patients with HA or HB without inhibitor is based on data derived from a total of 180 unique participants with HA or HB with or without inhibitors who received at least one dose of marstacimab while enrolled in a clinical study including the Phase 1b/2 B7841002/B7841003 studies, the Phase 3 B7841005 study, and the long-term extension Study B7841007. A description of these studies are provided in [Table 3](#). For details on Study B7841005, see Section [6](#) and Section [15](#). None one of these studies included a simultaneous comparator arm.

The primary safety profile for marstacimab is based on safety data from the active treatment phase (ATP) of Study B7841005. As per study design, all participants regardless of treatment received during the OP (OP-OD and OP-PPX) received marstacimab prophylaxis during the ATP. There were 117 participants in these two cohorts who received at least one dose of marstacimab; however, one of these participants is excluded from the data set due to termination of the study site for Good Clinical Practice (GCP) noncompliance. This participant did not experience any AEs. Therefore, the primary safety population (PSP) comprises 116 participants, 33 from the OP-OD cohort and 83 from the OP-PPX cohort.

The safety analysis of the PSP is based on a pooled population of the two cohorts because whether participants received on-demand factor replacement or prophylaxis factor replacement prior to enrollment or during the observation period is not expected to impact the safety profile of marstacimab. Limited safety analyses for the PSP by cohort is provided in Section [17.2](#). This analysis did not identify any significant differences in safety based on type of factor treatment (on-demand or prophylaxis) received during the OP, and therefore, reporting in the USPI by prior factor therapy (i.e., by cohort) is not indicated.

Based on the similarity of the underlying mechanism of HA and HB and the mechanism of action of marstacimab, Study B7841005 did not enroll participants with HA and HB to separate cohorts. For this same reason, a safety analysis of the PSP by hemophilia type is not expected to be different in these two subpopulations. Thus, the primary safety analysis of the PSP is based on participants with HA and HB. A limited safety analysis by hemophilia subtype is provided in Section [17.2](#). The analysis did not identify any significant differences in safety based on type hemophilia, and therefore, reporting in the USPI by hemophilia type is not indicated.

An analysis of a pooled marstacimab integrated safety population (ISP) was performed to identify additional, rare safety signals that may become apparent only in a larger safety population. The ISP comprises 179 unique participants with HA or HB with or without inhibitor who received at least one dose of the marstacimab in Studies B7841005/B7841007 (n=151) and B7841002/B7841003 (n=28). Of the 151 participants from Studies B7841005/B7841007, 116 were without inhibitors and 35 with inhibitors. Of the 28 participants from Studies B7841002/B7841003, 19 were without inhibitors and 9 with inhibitors.

Three additional studies were reviewed individually for safety. This included six participants with hemophilia A or B from Phase 1 study, Study B7841010, and 60 healthy participants from Studies B7841009 and B7841001. Review of safety data from these participants did not identify any potential safety signals not identified from analysis of the PSP or the ISP.

HYMPAVZI (marstacimab-hncq) injection

The safety assessment performed on data from the ongoing B7841005 study had a cutoff date of April 17, 2023, for noninhibitors cohorts, and a cutoff date of March 10, 2023, for long term B7841007 study. Studies B7841002, a Phase 1b/2, and B7841003 long term treatment were completed. The 120-day safety update provided additional safety data collected from ongoing clinical studies, including study ongoing B7841005, long-term study B7841007 and pediatric Study B7841008, as of cutoff date of October 9, 2023.

Clinical study data were independently analyzed by the Agency. Clinical data scientists (CDSs) from the Division of Biomedical Informatics generated the safety tables and figures. These include safety tables and figures for participants disposition, exposure data, AEs, and serious adverse events (SAEs). Additional exploration and analysis of AEs were performed by the clinical reviewers using JMP, JMP Clinical, and the Office of Computational Science Medical Dictionary for Regulatory Activities (MedDRA)-based Adverse Event Diagnostics tool (MAED). The Applicant's translations of verbatim terms to the MedDRA (version 25.1) preferred terms (PTs) for the events reported in Study B7841005 were reviewed and found to be acceptable. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Treatment-emergent adverse events (TEAEs) were analyzed at all levels of the MedDRA hierarchy and using FDA Medical Queries (FMQ) narrow. FMQ (narrow) are a collection of approximately 110 standardized groups, where each group comprises adverse event terms that reflect a specific medical concept. Each FMQ term is composed of one or more PTs. FMQs are not mutually exclusive, that is an individual PT may be counted in more than one FMQ. When reporting FMQ analyses, all FMQs, including overlapping terms, are included in the presentation of the data in this review. In addition, not all PTs are included in an FMQ. To assure that all potential safety signals are identified, analysis of all reported TEAEs not included in at least one FMQ were identified and analyzed. These PTs were generally laboratory assessments or vital sign assessments.

- Review of safety was based upon:
- Clinical Study Report for studies
- Protocol for studies
- Data sets for the populations described above
- Summary of clinical safety
- 120-day safety update
- Patient narratives
- Case report forms
- Case report forms and narratives were provided and reviewed for SAEs, and adverse events of interest (AEIs)

7.5. Adequacy of the Clinical Safety Database

The exposure for the primary safety population is shown in [Table 28](#). The median duration of exposure was 358 (range 22 to 386) days. Among participants in the PSP, 97% were exposed to marstacimab for 6 months or longer, and 75% were exposed for at least 1 year.

Table 28. Duration of Exposure Active Treatment Phase, Primary Safety Population, Study B7841005

	Marstacimab N=116
Duration of treatment, days	
Mean (SD)	347.4 (53.1)
Median (Q1, Q3)	358 (353.8, 359)
Min, max	22, 386
Total exposure (person years)	110
Patients treated, by duration, n (%)	
≥0 to <60 days	1 (0.9)
≥60 to <120 days	3 (2.6)
≥120 to <180 days	0
≥180 to <240 days	0
≥240 to <300 days	1 (0.9)
≥300 to <360 days	87 (75)
≥360 to <400 days	24 (20.7)
≥400 days	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is active treatment phase: 12 months.

Abbreviations: max, maximum; min, minimum; N, number of participants in treatment arm; n, number of participants with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

In the ISP, the mean (SD) and median (Min, Max) marstacimab exposure were 447 (188) days and 454 (7, 847), respectively. Among participants in the ISP, 89% were exposed to marstacimab for 6 months or longer, and 78% were exposed for at least 1 year.

The size of the safety database is considered adequate for a comprehensive safety assessment of marstacimab for the proposed indication, patient population, dosage regimen, and duration, given the rarity of hemophilia. Although the analysis is based only single arm data, with no comparator, this is consistent with other drug development programs for hemophilia.

7.6. Safety Results

Overall, marstacimab was well tolerated, with few participants having serious side effects or requiring discontinuation or dose interruption, with a safety profile consistent with other approved anti-hemophilic agents. Safety analysis showed marstacimab to have an acceptable safety profile in both participants who received prior on-demand factor treatment or prophylactic treatment with factors replacement. The design of the study was such that each participant served as their own control during the observation period for efficacy but similar to other development programs for hemophilia, the study design did not allow for randomized controlled safety data.

Key safety findings of adverse event analyses of the ATP in Study B7841005 are:

- There were no fatal adverse events.
- Serious adverse events (SAEs) occurred in 6% of participants. The most common SAE, occurring in ≥ 2 participants, was hemorrhage which was considered likely related to underlying disease and unlikely to be related to marstacimab based on its mechanism of action (marstacimab is procoagulant agent) and disease of study.
- Adverse events leading to permanent discontinuation of marstacimab were rare, occurring in 2 (2%) participants. One participant discontinued treatment due to atypical meningioma and the other due to peripheral swelling.
- Dose interruption of marstacimab occurred in 13% of participants. The most common AEs leading to dose interruption, occurring in $\geq 2\%$ of participants, was COVID-19 infection (10%).
- The most common adverse events, based on narrow FMQ, occurring in $\geq 5\%$ of participants, were viral infection (21%), local administration reactions (10%), hemorrhage (10%), nasopharyngitis (9%), headache (7%) and pruritus (7%).

7.6.1. Safety Results, Active Treatment Phase, Study B7841005

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Active Treatment Phase

[Table 29](#) provides an overview of TEAEs, based on frequency analysis of the PSP receiving marstacimab prophylaxis during the active treatment phase for Study B7841005.

During treatment with marstacimab, approximately two-thirds of participants experienced at least one TEAE. Most TEAEs were mild or moderate in severity with only 5% of participants having a severe AE. There were no AEs leading to death during the ATP. SAEs were reported in 7 (6%) participants. Permanent discontinuation due to TEAEs was reported in one participant, due to a need for meningioma. Interruption due to TEAEs was reported for 15 (13%) of participants, with most cases (12/15) due to COVID-19 infection.

Table 29. Overview of Adverse Events, Active Treatment Phase, Primary Safety Population, Study B7841005

Parameter	Marstacimab N=116 n (%)
Treatment-emergent adverse events	74 (64)
Severe and worse	6 (5.2)
Moderate	17 (14.7)
Mild	51 (44)
TEAE leading to death	0 (0)
Serious TEAEs	7 (6)
TEAE leading to permanent discontinuation	1 (0.9) ¹
TEAE leading to interruption	15 (12.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

Duration is 12 months in the active treatment phase.

Severity as assessed by the investigator

¹ One additional participant decided to withdraw from study rather than resume treatment after study drug was held for SAE of peripheral leg edema. The action taken with study drug for this TEAE was study drug held. (See Section 7.6.1.3 for further information).

Abbreviations: N, number of participants in treatment arm; n, number of participants with at least one event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths

There were no deaths reported in the Study.

7.6.1.3. Serious Treatment-Emergent Adverse Events

[Table 30](#) provides a frequency analysis of serious TEAEs, by system organ class and preferred terms, that occurred during ATP. There were 8 SAEs (tympanic membrane perforation, chest pain, peripheral swelling, tonsillitis, traumatic hemorrhage, hemarthrosis, meningioma, hemorrhage (one occurrence each) reported in 7 (6%) participants (one participant had two SAEs of chest pain and traumatic hemorrhage).

Table 30. Frequency of Serious Adverse Events by System Organ Class and Preferred Term, Active Treatment Phase, Primary Safety Population, Study B7841005

Parameter	Marstacimab N=116 n (%)
Serious adverse events	7 (6.0)
Ear and labyrinth disorders (SOC)	1 (0.9)
Tympanic membrane perforation	1 (0.9)
General disorders and administration site conditions (SOC)	2 (1.7)
Chest pain	1 (0.9)
Peripheral swelling	1 (0.9)
Infections and infestations (SOC)	1 (0.9)
Tonsillitis	1 (0.9)
Injury, poisoning and procedural complications (SOC)	1 (0.9)
Traumatic hemorrhage	1 (0.9)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.9)
Hemarthrosis	1 (0.9)

Parameter	Marstacimab N=116 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.9)
Meningioma	1 (0.9)
Vascular disorders (SOC)	1 (0.9)
Hemorrhage	1 (0.9)

Source: adae.xpt; Software: R

The active treatment phase includes all participants who received at least one dose of marstacimab.

Serious adverse events are defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is the active treatment phase: 12 months.

Abbreviations: incl, including; N, number of participants in treatment arm; n, number of participants with adverse event; SOC, system organ class

Analysis by narrow FMQ did not identify any safety signal not captured in the analysis by system organ class (SOC) and PT.

The SAEs of meningioma, tonsillitis, and tympanic membrane perforation were assessed by the investigator to be unrelated to marstacimab. Based on the mechanism of action of marstacimab, the review team concurs with this assessment.

The SAEs (PT level) of traumatic hemorrhage, hemorrhage, and hemarthrosis were considered by the investigator as unrelated to study drug. The review team concurs with this assessment and considered these events related to the underlying disease and unlikely to be related to treatment with marstacimab, based on its procoagulant mechanism of action.

- Participant (b) (6) is a 21-year-old male with HA who experienced the SAE of chest pain. On Day 159 of marstacimab, the participant experienced Grade 1 chest pain, which worsened to Grade 2 on Day 167, and resulted in hospitalization for atypical chest pain, cough, palpitation, and occasional dizziness. Extensive workup (including physical exam, electrocardiogram (ECG), D-dimer and troponin, CT angiography of pulmonary arteries, echocardiography, and MRI of brain with venogram) ruled out any cardiac, pulmonary, or brain etiology. The chest pain resolved 5 days later without intervention. Marstacimab treatment was not interrupted during the events. The Applicant assessed the event as not related to marstacimab treatment or any clinical study procedures. The review team assessed this SAE as unlikely to be related to marstacimab based on negative workup and resolution without study drug interruption.
- Participant (b) (6) is a 31-year-old male with HA, with history of synovectomy 15 months prior to start of marstacimab, who experienced right calf swelling on Day 24 of ATP prophylaxis treatment with marstacimab. The participant was hospitalized for the SAE of peripheral swelling with an initial diagnosis of cellulitis and marstacimab held. A doppler performed two days later showed no evidence of above the knee deep vein thrombosis (DVT). The event was resolved by Day 26. The participant declined restarting treatment with marstacimab and decided to withdraw from the study. The Applicant assessed this event as related to marstacimab. Although the doppler did not show evidence of a DVT, because the study was not performed until two days after hospitalization, the review team concluded it could not rule out DVT and based on marstacimab mechanism of action assessed the event as at least possibly related to marstacimab.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation and Interruptions

Adverse events leading to permanent treatment discontinuation were uncommon during ATP, occurring in only one participant (0.9%) who was diagnosed with an atypical meningioma and required surgery. Participant (b) (6), described above with right calf swelling, is not included as having discontinued due to AE as the narrative indicated discontinuation of study treatment was participant's choice and the event was not coded by the investigator as leading to discontinuation.

Dose reduction or interruption of marstacimab due to adverse events occurred in 13% of participants. The most common, occurring in $\geq 2\%$ of participants was COVID-19 infection (10%). Drug discontinuation rates were low, supporting the tolerability of marstacimab.

7.6.1.5. Treatment-Emergent Adverse Events

[Table 31](#) presents TEAEs occurring in $\geq 2\%$ of participants during the ATP treatment with marstacimab, based on PT. Overall, 65% of participants experienced at least one TEAE. The most common TEAEs, occurring in ≥ 5 participants were COVID-19 (17%), headache (6%), contusion (4%) and hypertension (4%).

Table 31. Frequency ($\geq 2\%$) of Treatment-Emergent Adverse Events by Preferred Term, Active Treatment Phase, Primary Safety Population, Study B7841005

Preferred Term	Marstacimab
	N=116 n (%)
Treatment-emergent adverse event	74 (63.8)
COVID-19	20 (17.2)
Headache	7 (6.0)
Contusion	5 (4.3)
Hypertension	5 (4.3)
Dental caries	4 (3.4)
Injection site pruritus	4 (3.4)
Pruritus	4 (3.4)
Tonsillitis	4 (3.4)
Arthralgia	3 (2.6)
Fibrin D dimer increased	3 (2.6)
Hemorrhoids	3 (2.6)
Injection site erythema	3 (2.6)
Prothrombin fragment 1.2 increased	3 (2.6)
Upper respiratory tract infection	3 (2.6)
Back pain	2 (1.7)
Diarrhea	2 (1.7)
Fall	2 (1.7)
Fatigue	2 (1.7)
Hematoma	2 (1.7)
Head injury	2 (1.7)
Herpes zoster	2 (1.7)
Injection site pain	2 (1.7)
Injection site swelling	2 (1.7)
Joint range of motion decreased	2 (1.7)

	Marstacimab N=116 n (%)
Preferred Term	
Muscle spasms	2 (1.7)
Pain in extremity	2 (1.7)
Peripheral swelling	2 (1.7)
Pharyngitis	2 (1.7)
Pyrexia	2 (1.7)
Rhinitis	2 (1.7)
Rhinitis allergic	2 (1.7)
Tooth fracture	2 (1.7)

Source: adae.xpt; Software: R

Primary Safety Population defined as all participants who received at least one dose of marstacimab during the active treatment phase.

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

Active treatment phase duration is 12 months.

Coded as MedDRA preferred terms.

Abbreviations: COVID-19, coronavirus disease of 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event

[Table 32](#) provides the frequency of TEAEs, occurring in $\geq 2\%$ of participants, by SOC and FMQ (narrow) in the safety population during the ATP prophylaxis treatment with marstacimab.

Table 32. Frequency of Treatment-Emergent Adverse Events (Occurring in ≥ 2 Participants) by System Organ Class and FDA Medical Query (Narrow), Active Treatment Phase, Primary Safety Population, Study B7841005

System Organ Class Preferred Term	Marstacimab N=116 n (%)
Blood and lymphatic system disorders (SOC)	
Anemia	2 (1.7)
Cardiac disorders (SOC)	
Systemic hypertension	5 (4.3)
Gastrointestinal disorders (SOC)	
Diarrhea	2 (1.7)
General disorders and administration site conditions (SOC)	
Local administration reaction	11 (9.5)
Fall	2 (1.7)
Fatigue	2 (1.7)
Peripheral edema	2 (1.7)
Pyrexia	2 (1.7)
Infections and infestations (SOC)	
Viral infection	24 (20.7)
Nasopharyngitis	10 (8.6)
Bacterial infection	4 (3.4)
Metabolism and nutrition disorders (SOC)	
Lipid disorder	3 (2.6)
Musculoskeletal and connective tissue disorders (SOC)	
Arthralgia	3 (2.6)
Fracture	3 (2.6)
Arthritis	2 (1.7)
Back pain	2 (1.7)
Tendinopathy	2 (1.7)

System Organ Class Preferred Term	Marstacimab N=116 n (%)
Nervous system disorders (SOC)	
Headache	8 (6.9)
Psychiatric disorders (SOC)	
Anxiety	2 (1.7)
Skin and subcutaneous tissue disorders (SOC)	
Pruritus	8 (6.9)
Erythema	3 (2.6)
Rash	2 (1.7)
Vascular disorders (SOC)	
Hemorrhage	12 (10.3)

Source: adae.xpt; Software: R

Safety set is defined as those participants who received at least one dose of marstacimab during the active treatment phase.

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

Active treatment phase is 12 months.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: FMQ, FDA medical query; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred term; SOC, system organ class

Adverse Reactions

TEAEs occurring in $\geq 3\%$ of participants during treatment with marstacimab in the ATP based on FMQ (narrow) ([Table 32](#)), were viral infection (21%), local administration reaction (10%), hemorrhage (10%), nasopharyngitis (9%), headache (7%) and pruritus (7%), systemic hypertension (4%), and bacterial infection (3%).

The most common TEAEs based on PT, not subsumed by FMQ (narrow) events, are dental carries (3%) and tonsillitis (3%) ([Table 31](#)).

The TEAEs of viral infection, nasopharyngitis, bacterial infection, dental carries, tonsillitis, and hypertension were considered unlikely to be related to treatment with marstacimab based on the mechanism of drug, and therefore were not considered to be adverse reactions.

The most common adverse reactions reported in $\geq 3\%$ of participants and included in Section 6 of the USPI, are injection site reactions (10%), headache (7%), and pruritus (3%). The frequency of pruritis reported in the USPI excludes events reported with the PT injection site pruritis, which are included in the event injection site reaction.

7.6.1.6. Laboratory Findings

Routine monitoring of blood and urine, including complete blood count, clinical chemistries, and hepatic and renal evaluations, were obtained regularly at prespecified points throughout the study. This section presents a frequency-based analysis of laboratory assessments.

Chemistries

Frequency of abnormal laboratory values for chemistry assessments are shown in [Table 33](#).

There were no significant changes in laboratory assessments for total protein, serum albumin, blood urea nitrogen, sodium, calcium, potassium, chloride, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, estimated glomerular filtration rate (eGFR, using Modification of Diet in Renal Disease method for adult participants; eGFR using Ped Schwartz method for adolescent participants), reported in during active treatment with marstacimab.

The majority of abnormal values for chemistry laboratory parameters were below level 2. Abnormal values $\geq$ level 3 were not observed for any analyzed chemistries reported in the table. Abnormal values above level 1 were rare, with the exception of low bicarbonate level 15 to <18 mEq/L was observed in 17% of participants during ATP. The minimum bicarb observed during the ATP across participants was 16.2 mEq/L. When evaluated at the participant level, only two participants had more than a single assessment <18 mEq/L. Based on TEAE reporting, neither of these participants had reasons for these lower bicarbonate values or evidence of sequelae. The review team concluded that the lower bicarbonate values observed in the participants were generally sporadic and not clinically significant.

Table 33. Frequency of Laboratory Values Exceeding Specified Levels for General Chemistry, Active Treatment Phase, Primary Safety Population, Study B7841005

Marstacimab	
N=116	
Laboratory Parameter	n/N_w (%)
Sodium, low (mEq/L)	
Level 1 (<132)	1/116 (0.9)
Level 2 (<130)	1/116 (0.9)
Level 3 (<125)	0/116 (0)
Sodium, high (mEq/L)	
Level 1 (>150)	1/116 (0.9)
Level 2 (>155)	1/116 (0.9)
Level 3 (>160)	0/116 (0)
Potassium, low (mEq/L)	
Level 1 (<3.6)	8/116 (6.9)
Level 2 (<3.4)	1/116 (0.9)
Level 3 (<3)	0/116 (0)
Potassium, high (mEq/L)	
Level 1 (>5.5)	0/116 (0)
Level 2 (>6)	0/116 (0)
Level 3 (>6.5)	0/116 (0)
Chloride, low (mEq/L)	
Level 1 (<95)	3/116 (2.6)
Level 2 (<88)	1/116 (0.9)
Level 3 (<80)	0/116 (0)

Laboratory Parameter	Marstacimab N=116 n/N_w (%)
Chloride, high (mEq/L)	
Level 1 (>108)	4/116 (3.4)
Level 2 (>112)	0/116 (0)
Level 3 (>115)	0/116 (0)
Bicarbonate, low (mEq/L)	
Level 1 (<20)	58/115 (50.4)
Level 2 (<18)	20/115 (17.4)
Level 3 (<15)	0/115 (0)
Bicarbonate, high (mEq/L)	
Level 3 (>30)	0/115 (0)
Calcium, low (mg/dL)	
Level 1 (<8.4)	1/116 (0.9)
Level 2 (<8)	0/116 (0)
Calcium, high (mg/dL)	
Level 1 (>10.5)	1/116 (0.9)
Level 2 (>11)	0/116 (0)
Albumin, low (g/dL)	
Level 1 (<3.1)	0/115 (0)
Level 2 (<2.5)	0/115 (0)
Blood urea nitrogen, high (mg/dL)	
Level 1 (>23)	4/116 (3.4)
Level 2 (>27)	0/116 (0)

Source: adlb.xpt; Software: R.

Threshold levels 1, 2, and 3 as defined in the Standard Safety Tables and Figures Integrated Guide.

Duration: Active treatment phase is 12 months.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data

Hematology Laboratory Findings

Frequency of abnormal laboratory values for chemistry assessments are shown in [Table 34](#).

There were no significant changes from baseline in hematological tests of lymphocytes, hemoglobin, platelet counts, neutrophil and eosinophil during ATP.

Table 34. Frequency of Laboratory Values for Hematology Analyte Values Exceeding Specified Levels, Active Treatment Phase, Primary Safety Population, Study B7841005

Hematological Laboratory Parameter	Marstacimab N=116 n/N_w (%)
WBC, low (10 ³ cells/μL)	
Level 1 (<3.5)	11/116 (9.5)
Level 2 (<3)	7/116 (6.0)
Level 3 (<1)	0/116 (0)
WBC, high (10 ³ cells/μL)	
Level 1 (>10.8)	4/116 (3.4)
Level 2 (>13)	2/116 (1.7)
Level 3 (>15)	0/116 (0)

Hematological Laboratory Parameter	Marstacimab N=116 n/N_w (%)
Hemoglobin, low (g/dL)	
Level 2 (>1.5 g/dL dec. from baseline)	11/112 (9.8)
Level 3 (>2 g/dL dec. from baseline)	7/112 (6.2)
Platelets, low (10 ³ cells/μL)	
Level 1 (<140)	5/116 (4.3)
Level 2 (<125)	3/116 (2.6)
Level 3 (<100)	0/116 (0)
Lymphocytes, low (10 ³ cells/μL)	
Level 1 (<1)	10/116 (8.6)
Level 2 (<0.75)	2/116 (1.7)
Level 3 (<0.5)	0/116 (0)
Lymphocytes, high (10 ³ cells/μL)	
Level 1 (>4)	2/116 (1.7)
Level 2 (>10)	1/116 (0.9)
Level 3 (>20)	0/116 (0)
Neutrophils, low (10 ³ cells/μL)	
Level 1 (<2)	18/116 (15.5)
Level 2 (<1)	4/116 (3.4)
Level 3 (<0.5)	0/116 (0)

Source: adlb.xpt; Software: R.

Threshold levels 1, 2, and 3 as defined in the Standard Safety Tables and Figures Integrated Guide.

Duration: Active treatment phase is 12 months.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: dec., decrease; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal; WBC, white blood cells

Coagulation Laboratory Findings

There were no clinically meaningful findings related to coagulation studies, including prothrombin time, aPTT, fibrinogen, and antithrombin levels.

Liver Laboratory Findings

[Table 35](#) presents abnormal liver laboratory findings by maximum worsening grade during the ATP prophylaxis with marstacimab. There were no clinically meaningful differences in liver tests during the active treatment phase prophylaxis treatment with marstacimab.

Table 35. Liver Function Laboratory Test Abnormalities, Worsened Postbaseline Level, Active Treatment Phase, Primary Safety Population, Study B7841005

Laboratory Test	Marstacimab N=116 n/N_w (%)
Alkaline phosphatase, high (U/L)	
Level 1 (>1.5X ULN)	0/116 (0)
Level 2 (>2X ULN)	0/116 (0)
Level 3 (>3X ULN)	0/116 (0)

Laboratory Test	Marstacimab N=116 n/N_w (%)
Alanine aminotransferase, high (U/L)	
Level 1 (>3X ULN)	0/116 (0)
Level 2 (>5X ULN)	0/116 (0)
Level 3 (>10X ULN)	0/116 (0)
Aspartate aminotransferase, high (U/L)	
Level 1 (>3X ULN)	0/116 (0)
Level 2 (>5X ULN)	0/116 (0)
Level 3 (>10X ULN)	0/116 (0)
Bilirubin, total, high (mg/dL)	
Level 1 (>1.5X ULN)	1/116 (0.9)
Level 2 (>2X ULN)	1/116 (0.9)
Level 3 (>3X ULN)	1/116 (0.9)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration during the active treatment phase is 12 months.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal.

7.6.1.7. Assessment of Drug-Induced Liver Injury

[Table 36](#) and [Figure 11](#) show screening assessment for potential cases of serious drug-induced liver injury in Study B7841005. No potential cases met Hy's Law criteria or are seen in Temple's Corollary quadrants of the hepatocellular scatterplots (eDISH) during ATP in Study B7841005. There was only one case in the cholestasis quadrant. This participant (b) (6) had evidence of cholestasis as manifested by maximum total bilirubin of 3.2 x ULN without elevated liver enzymes. This participant had an elevated bilirubin at baseline and a diagnosis of Gilbert's syndrome.

Table 36. Participants in Each Quadrant With Potential Hepatocellular Drug-Induced Liver Injury Screening Plot, Active Treatment Phase, Primary Safety Population, Study B7841005

Quadrant	Marstacimab N=116 n/N_w (%)
Potential Hy's law (right upper)	0/116 (0)
Cholestasis (left upper)	1/116 (0.9)
Temple's corollary (right lower)	0/116 (0)
Total	1/116 (0.9)

Source: adlb.xpt; Software: R

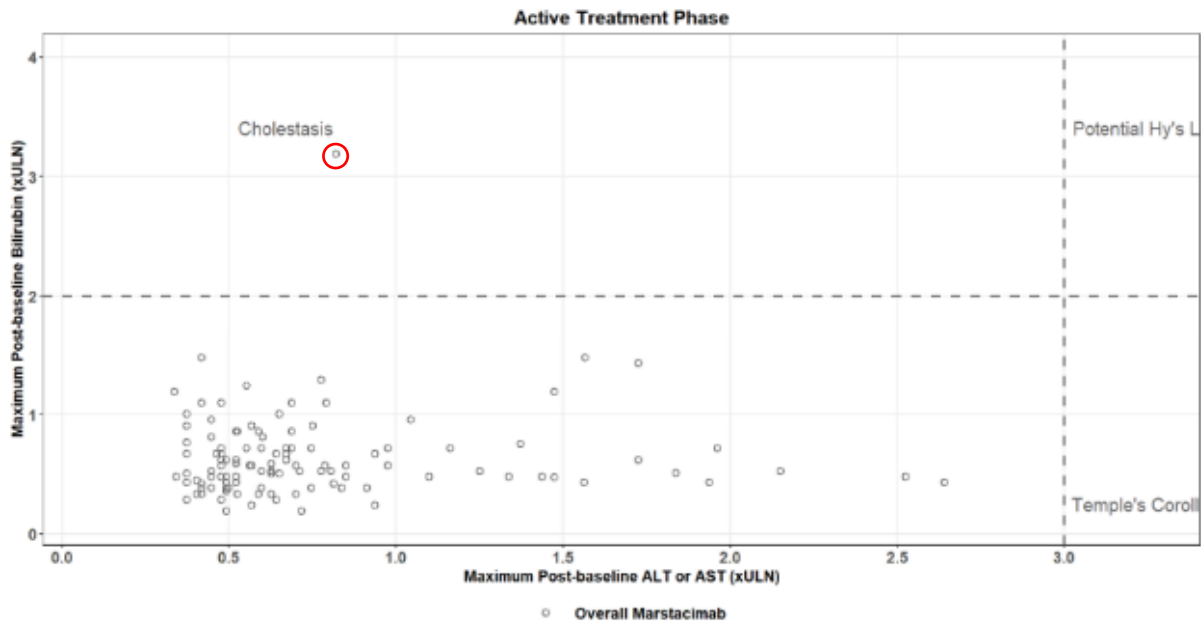
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transferase; DILI, drug-induced liver injury; N, number of participants in treatment arm; n, number of participants meeting criteria; N_w, number of participants with data; ULN, upper limit of normal

[Figure 11](#) shows a screening assessment for potential cases of serious drug-induced liver injury.

Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Active Treatment Phase, Primary Safety Population, Study B7841005



Source: adlb.xpt; Software: R

Primary safety population defined as all participants who received at least one dose of marstacimab during the active treatment phase.

Each data point represents a participant plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.

A potential Hy's law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All participants with at least one post-baseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

7.6.1.8. Vital Signs' Analyses

Analysis of vital signs for Study B7841005 during the ATP did not identify any clinically meaningful changes from baseline values for body temperature, pulse or respiration rate, or blood pressure.

7.6.1.9. Subgroup Analyses

Section 17.1 presents an analysis of adverse events by hemophilia type (HA versus HB). The analysis did not identify any significant differences in TEAS overall or by PT and SOC between hemophilia type.

Table 37 summarizes subgroup analyses for SAEs reported in Study B7841005 during ATP. No conclusions can be drawn from any differences among groups based on age, race, or ethnicity due to the small number in each subgroup and low incidence of SAEs in the study.

Table 37. Frequency of Serious Adverse Events by Demographic Subgroup, Active Treatment Phase, Primary Safety Population, Study B7841005

Parameter	Marstacimab N=116 n/N _w (%)
Sex	
Male	7/116 (6)
Age group, years	
Group 1 (12 to <18)	1/19 (5.3)
Group 2 (18 to 44)	5/70 (7.1)
Group 3 (45 to 64)	1/26 (3.8)
Group 4 (≥65)	0/1 (0%)
Race	
Black or African American	0/1 (0)
White	4/56 (7.1)
Asian	3/58 (5.2)
Missing	0/1 (0)
Ethnicity	
Hispanic or Latino	1/12 (8.3)
Not Hispanic or Latino	6/104 (5.8)

Source: xpt; Software: R.

Primary Safety population defined as all participants who received at least one dose of marstacimab during the active treatment phase.

Abbreviations: N, number of participants in treatment arm; n, number of participants with serious adverse event; N_w, number of participants in subgroup

Table 38 summarizes subgroup analyses for TEAEs reported in Study B7841005 during ATP. There were no significant differences in the occurrence of TEAEs based on age groups, race, ethnicity, or hemophilia type in the study.

Table 38. Frequency of Adverse Events, by Demographic Subgroup, Active Treatment Phase, Primary Safety Population, Study B7841005

Characteristic	Marstacimab N=116 n/N _w (%)
Sex	
Male	74/116 (63.8)
Age group, years	
<18	13/19 (68.4)
18 to 44	39/70 (55.7)
45 to 64	21/26 (80.8)
65 to 74	1/1 (100)

Characteristic	Marstacimab N=116 n/N_w (%)
Age group ≥65, years ≥65	1/1 (100)
Age group ≥75, years ≥75	0/116 (0)
Race	
Asian	35/58 (60.3)
Black or African American	0/1 (0)
White	38/56 (67.9)
Missing	1/1 (100)
Ethnicity	
Hispanic or Latino	6/12 (50)
Not Hispanic or Latino	68/104 (65.4)
Country	
United States	1/1 (100)
Non-United States	73/115 (63.5)
Hemophilia type	
Hemophilia A	57/91 (62.6)
Hemophilia B	17/25 (68)

Source: adae.xpt; Software: R

Primary Safety Population defined as all participants who received at least one dose of marstacimab during the active treatment phase.

Abbreviations: N, number of participants in treatment arm; n, number of participants with adverse event; N_w, number of participants in subgroup

Adverse Events in Subgroup of Patients Who Receive Dose Escalation to 300 mg QW

Marstacimab dose escalation from 150 mg SC QW to 300 mg SC QW was allowed after 6 months treatment with marstacimab during ATP Day 180 (Visit 14), if a participant met the protocol-specified dose escalation criteria of weighing at least 50 kg and having two or more spontaneous (atraumatic) bleeds of joint bleeds or significant soft tissue/muscle or other site bleed, treated with infusion(s) of FVIII or FIX over a 6-month period in the absence of a confirmed FVIII or FIX inhibitor.

In Study B7841005, a total of 14 participants had marstacimab dose escalation from 150 mg QW to 300 mg QW. The mean (SD) exposure for the 14 participants who received 300 mg QW marstacimab during ATP was 118.6 days (56.3), and the median exposure was 116.5 days.

In these participants, while receiving marstacimab 300 mg during ATP, there were no TEAEs that led to discontinuation or SAEs. A total of 5 TEAEs were reported in 5 out of the 14 participants (36%) after escalation to the higher dosage of 300 mg QW:

- Two participants experienced a TEAE of arthralgia on Study Day 190 and Day 252.
- One participant experienced a TEAE of joint range of motion reduction on Study Day 183.
- One participant experienced a TEAE of laryngitis on Study Day 205.
- One participant experienced a TEAE of rhinitis on Study Day 191.

Overall, the frequency of TEAEs was 36% in participants when receiving a dosage of 300 mg QW compared to 64% of all participants when receiving 150 mg QW. We note, however, that no

conclusion can be drawn about this observed difference as the study was not designed to compare the safety of two doses, and the number of participants who required dose escalation was small with shorter duration of exposure compared to the duration of exposure in most participants receiving 150 mg QW dosage.

7.6.2. Safety Results, Integrated Safety Population Assessment

To identify potential rare AEs that might be detectable only in a larger dataset, we performed an analysis of the ISP, comprising 180 participants with HA or HB (see Section 7.4) Analysis of the ISP considered only AEs occurring while participants were receiving marstacimab.

There were no deaths in any of the reviewed marstacimab studies.

The 120-day safety update was consistent with the original safety analysis.

Thromboembolic Events

There were no thromboembolic events in the ISP. There were no events of thrombotic microangiopathy or disseminated intravascular coagulopathy/consumption coagulopathy in any study in the marstacimab development program. There was one case of a thromboembolic event that occurred in a healthy participant enrolled in a bioequivalence study. This case is discussed in Section 7.6.3).

Drug Hypersensitivity

There were no reported cases of anaphylaxis, Stevens Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms, or toxic epidermal necrolysis in the ISP. There was one TEAE event of urticaria that was incorrectly coded under PT "Anaphylaxis." This event resolved without sequelae after treatment with oral antihistamine and the participant continued treatment.

A total of 11 participants had reports at least an event of the preferred term hypersensitivity (see Drug Hypersensitivity in Section 7.6.3 for more details).

Hy's Law

The analysis performed on the ISP did not reveal any cases that met the criteria of Hy's Law.

7.6.3. Adverse Events of Special Interest

The Applicant identified the following adverse events of special interest (AESIs) based mechanism of action, safety profiles of other drugs in same class, experience in early phase clinical studies of marstacimab, events that may require additional monitoring or treatment modification: injection site reactions, thromboembolic events, liver toxicity, and hemorrhage. In addition, COVID-19 was designated as an AESI due to the potential to increase the risk of thrombotic events. Table 39 summarizes the frequency of thromboembolic events, hemorrhage, injection site reactions, hypersensitivity reaction, and hypertension.

Table 39. Frequency of Adverse Events of Special Interest, Active Treatment Phase, Primary Safety Population, Study B7841005

Adverse Event	Marstacimab N=116 n (%)
Thrombotic and embolic TEAE (SMQ)	0 (0)
Hemorrhage TEAE (SMQ)	13 (11.2)
Contusion	5 (4.3)
Hemorrhage	3 (2.6)
Hematoma	2 (1.7)
Hemarthrosis	2 (1.7)
Epistaxis	1 (0.9)
Injection site reactions ¹	11 (9.5)
Peripheral swelling	2 (1.7)
Injection site erythema	3 (2.6)
Injection site pruritus	4 (3.4)
Injection site hematoma/bruising	3 (2.6)
Injection site pain	2 (1.7)
Injection site induration	1 (0.9)
Hypersensitivity (SMQ)	8 (6.9)
Pruritus	4 (3.4)
Rhinitis allergic	2 (1.7)
Eczema	1 (0.9)
Rash	1 (0.9)
Hypertension (SMQ)	5 (4.3)

Source: adae.xpt; Software: R

¹ Group query Injection site reactions comprise the PT: injection site pruritus, injection site swelling, injection site erythema, injection site bruising, injection site induration, injection site pain, injection site edema, injection site hematoma.

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of participants in treatment arm; n, number of participants with adverse event; PT, preferred term; SMQ, s tandardized MedDRA query; TEAE, treatment-emergent adverse event

Thromboembolic Events

Thromboembolic events were considered an AESI due the mechanism of action of the drug as a thrombogenic agent and the increased risk of thromboembolic events observed with other anti-hemophilic drugs. Marstacimab has not been studied in patients with a history of previous thromboembolic events (patients with history of thromboembolic events were excluded from marstacimab studies).

During the marstacimab development program clinical studies, one healthy participant, who received marstacimab while participating in the bioequivalence Phase 1 Study B7841009, developed a thromboembolic event of pulmonary embolism and probable deep vein thrombosis of the right posterior tibial vein 9 days after first receiving marstacimab and 29 days after vaccination with the second dose of the AstraZeneca (ChAdOx1-S [recombinant] vaccine) COVID-19 vaccine. The participant discontinued the study due to the event. The event resolved and was considered related to marstacimab.

There were no participants with hemophilia across the development program who reported thromboembolic events during prophylactic treatment with marstacimab. One participant reported a Grade 2 (nonserious) hemorrhoid thrombosed which was considered by the investigator as possibly related to marstacimab treatment; however, the event of hemorrhoid thrombosed was attributed to local inflammation and not related to any thromboembolic event.

There were no thrombotic microangiopathy events reported in marstacimab development program.

The risk of thromboembolic events is included in Warnings and Precautions of the USPI based on class labeling. Due to the small size of the safety database and limited duration of exposure for a drug that will be administered chronically, the Division recommended enhanced pharmacovigilance for thromboembolic events be implemented at the time of approval.

Injection Site Reactions

Injection site reactions were considered an AESI based on the occurrence with drugs in the related classes. In Study B7841005, injection site reaction was reported in 11 (10%) participants during ATP prophylaxis treatment with marstacimab. The majority of injection site reactions were Grade 1 (10 participants). One participant reported 70 events of Grade 1 or 2 AEs associated with injection, mostly as injection site pruritus, erythema, or induration. This participant tested positive for neutralizing antibody (NAb) at Day 120. None of the injection site reactions were serious or led to permanent discontinuation.

Injection site reactions were more frequent 9/26 (35%) in Study B7841002 where participants received higher doses (150, 300, 450 mg) for 3 months. Most events were mild (six participants). Severe injection site reactions were reported in two participants (one injection site pain, one injection site swelling) who received 450 mg SC QW (1.5 mL injection volume).

Drug Hypersensitivity

In Study B7841005, hypersensitivity adverse events were reported in eight (6.9%) participants during ATP prophylaxis treatment with marstacimab. None of these were severe or systemic cases of hypersensitivity or anaphylaxis.

In the ISP analysis, three participants in Study B7841005 with hemophilia with inhibitors reported events of stomatitis, rash, and anaphylactic reaction. One participant with HB with inhibitor experienced a SAE of papular skin urticaria over the entire body (except head and neck). The event was considered related to marstacimab, and the drug was discontinued. The diagnosis was confirmed by three skin biopsies performed on three separate occasions, and the participant was treated with systemic corticosteroids. A second participant experienced an adverse event urticaria which was reported by the investigator as “Anaphylaxis” (Reported Term for the Adverse Event [AETERM]). The participant was treated with one tablet (a single dose) of loratadine and resolved without sequelae. The participant continued with their weekly dose of 150 mg marstacimab without further reaction. A third participant experienced an adverse event of stomatitis which was considered related to marstacimab.

Hypersensitivity is included in Warnings and Precautions of the USPI.

7.6.4. QT-IRT Study Review

A thorough QT study was not conducted in humans. There were no clinically important changes in ECGs observed in Study B7841005. No participants experienced postdose QTcF values ≥ 480 msec.

7.7. Key Safety Review Issues

No safety review issues were found.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Based on the population PK analysis, no clinically significant differences in the pharmacokinetics of marstacimab were observed based on race (Asian or non-Asian), hemophilia type (A and B), mild renal impairment (eGFR of 60 to 89 mL/min/1.73 m²), and hepatic function as defined by total bilirubin $1\times$ to $\leq 1.5\times$ ULN.

Body weight was identified as a significant covariate impacting the pharmacokinetics of marstacimab, and therefore was included as a structural covariate in the popPK final model (refer to Section [14.5](#) for details). The popPK results showed that weight accounted for most of the observed differences between adults and adolescents (i.e., the difference in clearance decreased from 28.8% to 3.1% when accounted for body weight difference). Similarly, the difference of clearance values decreased between healthy and hemophilia participants (19.9% to 12.1%) and Asian and non-Asians (34.6% to 31.9%) when adjusted for body weight.

No dedicated studies have been conducted to evaluate the impact of renal or hepatic impairment. As marstacimab is a monoclonal antibody that is expected to be metabolized by catabolic pathway and receptor-mediated clearance, the pharmacokinetic is not expected to be different in participants with renal or hepatic impairment.

8.2. Extrinsic Factors

No clinical drug-drug interaction (DDI) study was conducted with marstacimab. As marstacimab is a monoclonal antibody, PK-based DDI is unlikely to occur.

In vitro DDI studies were performed with marstacimab and bypass agents such as recombinant Factor VIIa (rFVIIa) and aPCC in plasma of participants with hemophilia using thrombin generation assay (TGA). The studies showed that there was no additive effect when marstacimab was used in combination with rFVIIa. While thrombin level increased when marstacimab was used in combination with aPCC compared to marstacimab alone, it was still within the range of marstacimab used in nonhemophilic plasma, which would have full complement of coagulation

factors. Therefore, bypassing agents can be used in cases of breakthrough bleeds while patients are on marstacimab.

8.3. Plans for Pediatric Drug Development

Animal Data

Dedicated juvenile animal studies have not been conducted with marstacimab.

8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential

8.4.1. Animal Data

The following nonclinical information was used in support of the indicated labeling sections. Additional nonclinical details are in Section [13](#).

Table 40. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Pregnancy: Reproduction studies have not been conducted in female animals based on target patient population being limited to male subjects. Hemophilia A and B are X-linked inherited blood clotting disorder which occurs predominantly in males and is extremely rare in females. Since the risk to female patients is minimal but not absent, recommendation to include the use of contraception is advisable.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	The carcinogenicity potential of marstacimab has not been assessed. Based on weight of evidence analysis, marstacimab is highly unlikely to pose a significant cancer risk to humans. Genotoxicity of marstacimab was not appropriate because marstacimab is a protein and considered devoid of direct genotoxic risk. In a fertility and early embryofetal development study in marstacimab-treated male rats mated with naïve females, doses up to 1000 mg/kg/week had no effect on any of the reproductive parameters (volume of the testis, total sperm count, sperm motility or sperm morphology). Treated males successfully mated with untreated female rats. There were no findings in conceptuses (number of viable embryos, total resorptions, pre- or post-implantation loss). The highest intravenous dose of 1000 mg/kg/week was considered the NOAEL (>200 times the MRHD AUC exposure). Female fertility studies were not conducted with marstacimab.

Source: Derived from Applicant's data

Abbreviations: AUC, area under the concentration-time curve; MRHD, maximum recommended human dose

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed BLA 761369 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, the Office of Pharmaceutical Quality recommends approval of this BLA from a quality perspective.

9.1. Device or Combination Product Considerations

Marstacimab is provided as a 150 mg/mL solution for injection in either a single-dose prefilled syringe (PFS) or prefilled pen (PFP) for single use for subcutaneous administration. Each prefilled syringe or pen are designed to deliver 150 mg of marstacimab-hncq in 1 mL of solution. Marstacimab is supplied in carton that contains either one single-dose Type I glass prefilled syringe with a plunger stopper (chlorobutyl elastomer) or one single-dose prefilled pen with glass syringe inside the pen with needle guard. In addition, each carton contains stainless steel 27 gauge, ½ inch staked needle with a rigid needle shield (thermoplastic elastomer).

The Center for Devices and Radiological Health was consulted for evaluation of this product and found the product approvable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Study B7841005 was conducted in accordance with the principles of the Declaration of Helsinki Council, and International Conference on Harmonization GCP guidelines. An Independent Ethics Committee and/or Institutional Review Board reviewed approved and monitored the study. Signed written informed consent forms by participants or their legally authorized representative were required for study enrollment. A Clinical Site Inspection consult review was completed by Dr. Anthony Orencia in the Office of Scientific Investigations and is summarized below in Section [22](#). A Financial Disclosure summary review is located in Section [25](#).

11. Advisory Committee Summary

This application did not raise efficacy or safety issues requiring external expert advice. Therefore, an Advisory Committee meeting was not convened to discuss this application.

III. Additional Analyses and Information

12. Summary of Regulatory History

Marstacimab is a human monoclonal antibody directed against tissue factor pathway inhibitor (TFPI) that has been developed for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A (HA) (congenital factor VIII (FVIII) deficiency) without factor VIII inhibitors, or hemophilia B (HB) (congenital factor IX (FIX) deficiency) without factor IX inhibitors.

Marstacimab was granted orphan drug designation on May 18, 2016.

On November 18, 2016, FDA received a submission for a new IND application under Section 505(i) of the Federal Food, Drug, and Cosmetic Act (IND 126734). Prior to the IND submission, three meetings were held with the Applicant:

- Type B pre-IND meeting was held on August 6, 2015, to discuss the overall nonclinical and clinical development plan for marstacimab,
- Type C Written Responses were issued on May 11, 2016, to discuss the nonclinical development plan, and
- Type C Written Responses were issued on September 20, 2016, to discuss the appropriateness of design of the phase 1b/2 study.

On December 16, 2016, the Applicant was advised that the 30-day, safety review of the application had concluded and that the study may proceed with their proposed clinical investigation for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A or hemophilia B (with or without inhibitors).

Marstacimab was submitted for fast-track review twice. The first submission on May 15, 2017, was denied due to an inability to determine, based on the preclinical data provided and lack of clinical data, if marstacimab had the potential to meet an unmet medical need in patients with hemophilia who have inhibitors. The second review was submitted on July 19, 2019, for which the Applicant was granted fast track designation for marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia A with inhibitors or hemophilia B with inhibitors on September 17, 2019.

On September 21, 2017, a Type C guidance meeting was held to discuss the proposed clinical program to support initial registration of marstacimab for prophylaxis use in patients with hemophilia A and hemophilia B with inhibitors, and a subsequent submission to support prophylaxis use in patients with hemophilia A and hemophilia B patients without inhibitors.

On February 14, 2018, the Applicant requested a Type C meeting to discuss the quality and clinical proposed drug product development strategy for the commercial drug product (DP) presentations, including both prefilled syringe (PFS) and prefilled pen (PFP). This meeting request was subsequently withdrawn by the Applicant after receiving the FDA's preliminary

HYMPAVZI (marstacimab-hncq) injection

comments on May 23, 2018, stating that the Applicant planned to submit a Type C (Written Response Only) meeting request to gain further clarification in writing, relative to the FDA's preliminary comments and the acceptability of the Applicant's approach to implement Agency guidance.

On August 2, 2018, a Type C guidance meeting was held to seek agreement on key outstanding clinical development items from the September 2017, Type C meeting and to inform plans for a subsequent Type C meeting planned with FDA for October 2018 that would seek Agency endorsement of the full draft phase 3 pivotal study protocol. The FDA advised the Applicant during this meeting that there were concerns with the following:

- The proposal to switch patients without inhibitors who were on stable prophylactic regimens to marstacimab.
- The proposed number of subjects with HB was the minimum number of subjects needed to potentially support an indication and was likely not sufficient to adequately assess the safety and efficacy, given the potential for patient discontinuations and dropouts.
- The phase 3 protocol should specify the number of adolescent subjects (ages 12 to 18) to be enrolled and that a sufficient number of adolescent subjects would need to be enrolled to support an indication.

On August 15, 2018, written responses were issued to the Applicant to provide further clarification on the Type C meeting preliminary comments sent by the FDA on May 23, 2018, in regard to the quality and clinical proposals on the drug product development strategy for the commercial drug product (DP) presentations, including both PFS and PFP. The FDA informed the Applicant that their approach to product quality testing in PFS and PFP was not appropriate because they provided insufficient description of the planned characterization studies and testing plan. Further, the Applicant was informed that they needed to submit the Human Factors Validation study protocol for the 150 mg PFP presentation for Agency to review.

On October 23, 2018, a Type C guidance meeting was held to discuss the proposed Phase 3 pivotal study design, within the context of the described clinical development plan, in follow-up to the August 2, 2018, Type C meeting. The Applicant was informed during this meeting that the FDA had concerns with switching patients without inhibitors who are on stable prophylactic regimens to marstacimab.

On October 29, 2018, final written responses were issued to the Applicant to reach agreement with the FDA on key aspects of the quality and nonclinical development strategy. A key agreement made during this meeting was that the carcinogenic risk of marstacimab appeared low and carcinogenicity studies were not warranted at that time. However, it was recommended that the carcinogenicity assessment be submitted with the proposed BLA.

On March 5, 2020, a Type C guidance meeting was held to discuss the additional data provided from the completion of the phase 2 study, Study B7841002, and the interim analysis of the 12-month phase 2 extension study, Study B7841003 and whether or not the findings were sufficient to allow the inclusion of hemophilia A or B patients previously on stable factor prophylaxis therapy into the phase 3 study, B7841005. The FDA agreed that patients previously on stable

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HYMPAVZI (marstacimab-hncq) injection

prophylaxis could be included on the study but recommended that the Applicant submit the phase 3 protocol for review.

On December 6, 2021, a Type C guidance meeting was held to discuss the proposed statistical analysis plan and BLA submission strategy. The FDA expressed concerns with submitting only interim data analysis including but not limited to separate BLAs.

On May 9, 2022, the Applicant submitted a Type C meeting request to discuss the aspects of a planned BLA submission. This meeting request was cancelled by the Applicant after receiving the FDA's preliminary comments on July 20, 2022, stating the responses provided by the FDA were thorough and no further follow up was needed.

On November 1, 2022, Written Responses were issued to the Applicant to discuss chemistry, manufacturing, and controls specific questions in preparation for the BLA submission for licensure of marstacimab.

On June 21, 2023, a Type B, pre-BLA meeting request was held to discuss the proposed submission of a BLA for marstacimab. The Applicant was informed that it was unclear if the clinical package would be sufficient to support the submission of a BLA as the Applicant had not described a plan to demonstrate substantial evidence of effectiveness (SEE).

On September 5, 2023, the Applicant submitted a request for Breakthrough Therapy Designation Request Advice for the marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 6 months of age and older with: hemophilia A (congenital FVIII deficiency) with or without FVIII inhibitors, or hemophilia B (congenital FIX deficiency) with or without FIX inhibitors. The FDA informed the Applicant that there was insufficient information includes with the request for advice to determine if it was appropriate for the Applicant to submit breakthrough therapy designation request.

On October 5, 2024, the Applicant submitted a Breakthrough Therapy Designation Request for marstacimab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and pediatric patients 12 years of age and older with hemophilia A (congenital FVIII deficiency) without FVIII inhibitors, or hemophilia B (congenital FIX deficiency), without FIX inhibitors. The request was denied due to lack of clinical evidence indicating that marstacimab prophylaxis may demonstrate substantial improvements over existing therapies on one or more clinically significant endpoints.

FDA received BLA 761369 under Section 351(a) of the Public Health Service Act on October 11, 2023. The Applicant requested priority review. The application was accepted with no filing review issues. The application was set to be reviewed under a standard review timeline. The goal date for this application is October 11, 2024.

On April 3, 2024, the proprietary name Hympavzi was conditionally approved for marstacimab after a January 4, 2024, denial of the proposed name (b) (4) was denied because it may be confused with currently marketed (b) (4).

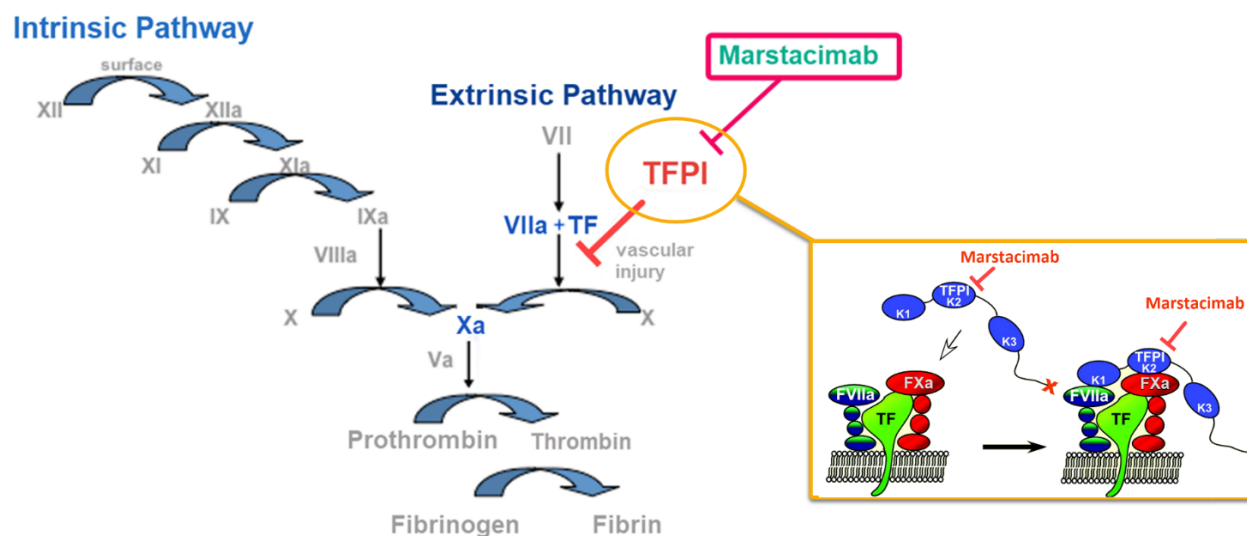
13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology (Primary and Secondary)

Tissue factor (TF) is a procoagulant protein located outside the vasculature that is released upon tissue injury to prevent excessive hemorrhage. Tissue factor pathway inhibitor (TFPI) is a plasma serine protease inhibitor of TF. Marstacimab (PF-06741086) is a fully humanized immunoglobulin G1 (IgG1) monoclonal antibody that targets the K2 domain of TFPI and reduces TFPI activity (see [Figure 12](#)). By blocking TFPI, marstacimab enhances TF activity and promotes the extrinsic coagulation process in participants with hemophilia A and B (i.e., those with genetic deficiency in the intrinsic coagulation pathway, in response to damage to the endothelial wall of blood vessels). Given that TF and TFPI are released outside the vasculature in response to injury, they are considered part of the extrinsic coagulation pathway. Both the extrinsic and intrinsic pathways converge on a common pathway beginning with the activation of factor X.

Figure 12. Schematic Pathway in the Coagulation Cascade and the Role of Marstacimab in the Extrinsic Pathway



Source: Modified figure of the Applicant and [Crawley and Lane \(2008\)](#)

Abbreviations: FVIIa, factor VIIa; FXa, factor Xa; K1, Kunitz domain 1; K2, Kunitz domain 2; K3, Kunitz domain 3; TF, tissue factor; TFPI, tissue factor pathway inhibitor

Inhibition and neutralization of TFPI in the extrinsic pathway by marstacimab is thought to reduce the negative feedback on FVIIa/TF/Factor X (FXa) complex, promoting free FXa to enter the common coagulation pathway to promote clot formation. By enhancing free FXa in a manner independent of the intrinsic pathway, marstacimab can provide an alternative treatment option for patients with both HA (FVIII deficiency) and HB (FIX deficiency).

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Marstacimab binds to TFPI at an epitope on the Kunitz-type domain K2 with similar affinity to the combined K1K2 domains (via K2), with a K_d of 2.63 and 3.7nM, respectively (Study #072904). Marstacimab has similar binding affinities to human, monkey, rabbit, rat, and mouse combined K1K2 domains ([Table 41](#)). Binding affinity of marstacimab to TFPI K2 of the combined K1K2 domains relative to concizumab). The triple Fc mutations caused marstacimab to have similar or lower binding to FcγR than an isotype control IgG1 monoclonal antibody (mAb) lacking effector function, suggesting that marstacimab also has negligible effector function (Study #15GR003).

TFPI is an endogenous serine protease inhibitor with at least three known Kunitz-type domains (K1, K2 and K3) separated by a short stretch of amino acids. TFPI is expressed by endothelial cells in α and β isoforms generated by alternative splicing of its pre-messenger RNA ([Huntington and Baglin 2018](#)). Mechanistic studies show marstacimab binds to the K2 domain of TFPI (Study #072904 & 121926). The enhanced coagulatory activity of marstacimab is based on binding to TFPI K2. By binding to TFPI K2, marstacimab prevents inactivation of both FXa and FVIIa, enhancing the extrinsic coagulation pathway, promoting hemostasis, and minimizing the need for FVIII or FIX. A comparative study of marstacimab to concizumab showed that concizumab is a nearly 7-fold more potent inhibitor of TFPI K2 in humans than concizumab. The binding affinity of marstacimab and concizumab to the combined K1K2 domains of TFPI is shown in [Table 41](#). Based on binding affinity, the Applicant predicted a clinically effective dose of between 100 to 300 mg marstacimab.

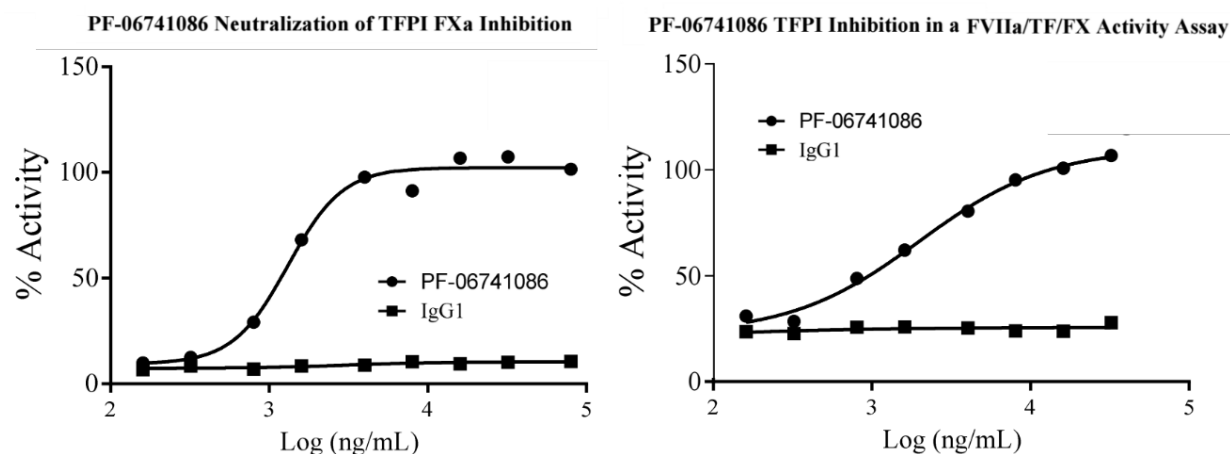
Table 41. Binding Affinity of Marstacimab to TFPI K2 of the Combined K1K2 Domains Relative to Concizumab

Product	Human K1K2	Rabbit K1K2
Marstacimab, nM	3.7	4.25
Concizumab, nM	0.493	1.81

Source: Derived from Applicant-provided data

Abbreviations: K1, Kunitz domain 1; K2, Kunitz domain 2; TFPI, tissue factor pathway inhibitor

In vitro studies show marstacimab can neutralize the K2 (half-maximal effective concentration [EC_{50}] of 1312 ng/mL or 8.75nM, marked by changes in FXa), and the combined TFPI K1K2 (EC_{50} =1985 ng/mL or 13.23nM) domains of TFPI in a dose-dependent manner relative to isotype control mAb ([Figure 13](#)).

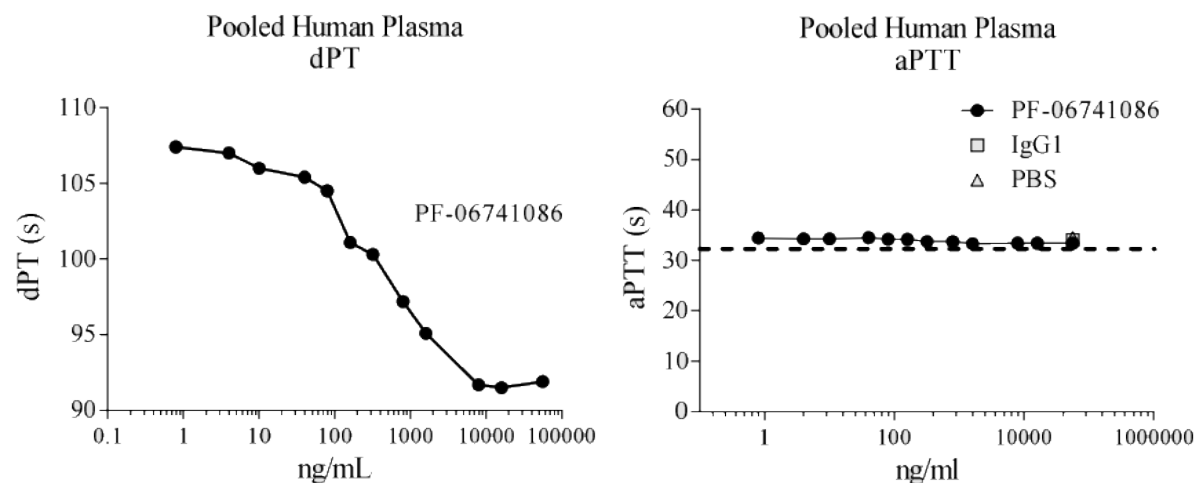
Figure 13. Marstacimab Dose-Dependent Inhibition of TFPI Activity on FXa and FVIIa/TF/FXa

Source: Applicant Study #085202

Abbreviations: FVIIa, factor VIIa; FX, factor X; FXa, factor Xa; IgG1, immunoglobulin G1; TF, tissue factor; TFPI, tissue factor pathway inhibitor

Marstacimab was effective in neutralizing TFPI activity in vitro in normal whole human blood, suggesting that it is likely to be effective in inhibiting TFPI (platelets and plasma) under normal coagulation conditions. There was a marstacimab-associated dose-dependent decrease in clotting time and clot formation time relative to an isotype control IgG1 mAb. The clot strength was not affected. The greatest activity was achieved at concentrations ≥ 16 $\mu\text{g/mL}$ marstacimab (Study #142056).

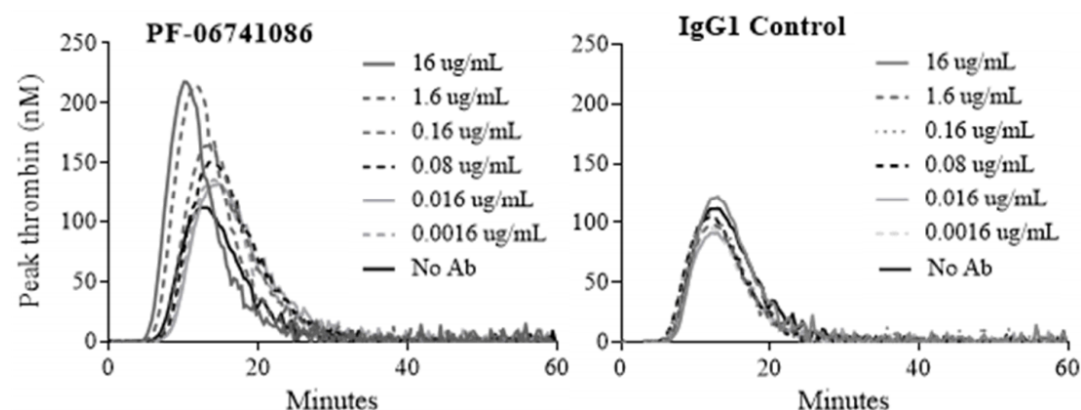
Platelet-poor plasma was generated by addition of citrate to plasma from healthy human volunteers, rabbits, and cynomolgus monkeys (Study #123404). Addition of marstacimab to nonhemophilic platelet-poor human plasma resulted in a dose-dependent decrease in diluted prothrombin time (dPT) ($\text{EC}_{50}=406$ ng/mL). There was no change in dPT in the isotype control group (IgG1 or phosphate buffered saline). Neither marstacimab nor the control treatment had any effect on activated partial thromboplastin time (aPTT) (Figure 14). A dose-dependent decrease in dPT clotting time was also observed in platelet-poor plasma of rabbits ($\text{EC}_{50}=629$ ng/mL) and monkeys ($\text{EC}_{50}=273$ ng/mL).

Figure 14. Marstacimab Effect on dPT (Seconds) and aPTT (Seconds) in Nonhemophilic Platelet-Poor Human Plasma

Source: Applicant Study #123404

Abbreviations: aPTT, activated partial thromboplastin time; dPT, diluted prothrombin time; IgG1, immunoglobulin G1; PBS, phosphate-buffered saline

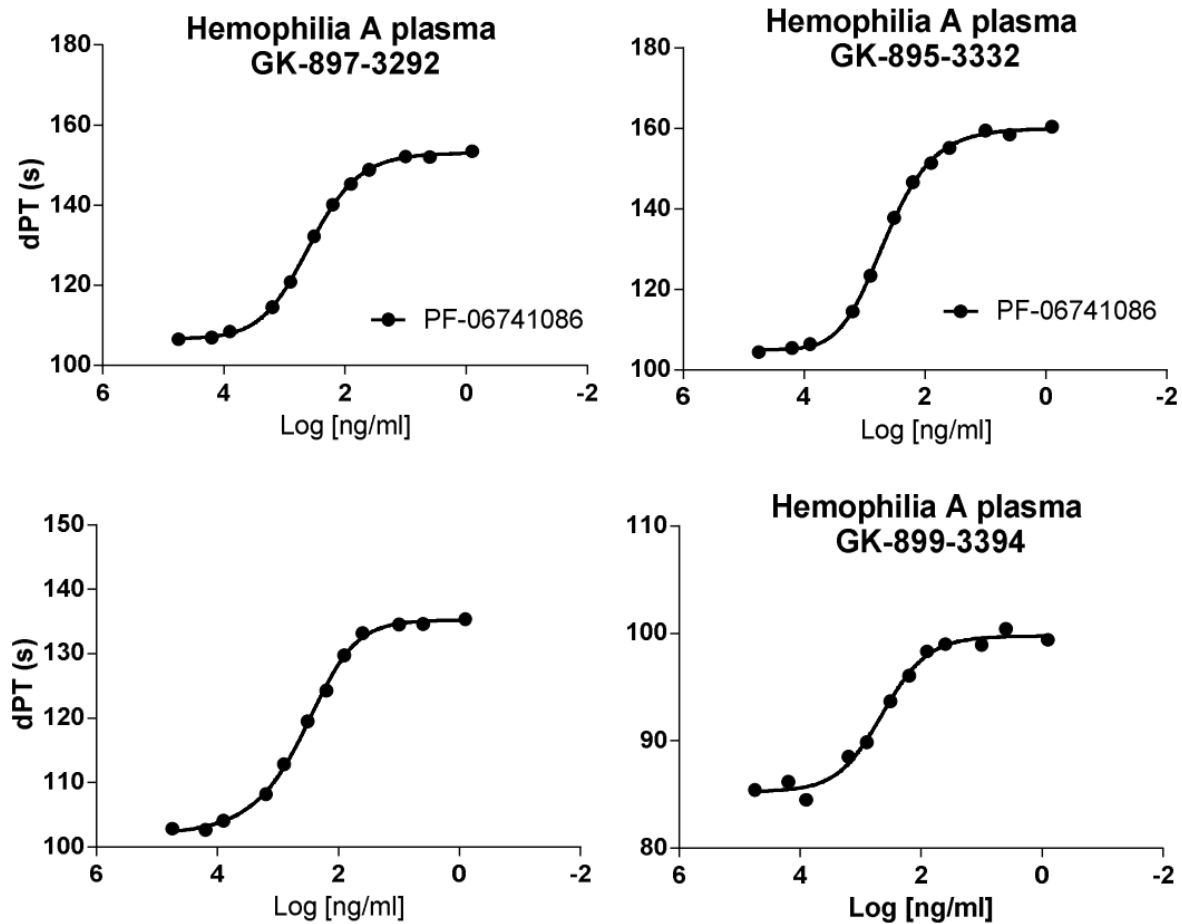
In the same study, marstacimab increased generation of thrombin time in platelet-poor plasma from nonhemophilic volunteers ([Figure 15](#)). These studies demonstrated that marstacimab has the potential to enhance coagulation pathway in patients with hemophilia.

Figure 15. Marstacimab Produced a Dose-Dependent Increase in Thrombin Generation in Nonhemophilic Platelet-Poor Human Plasma

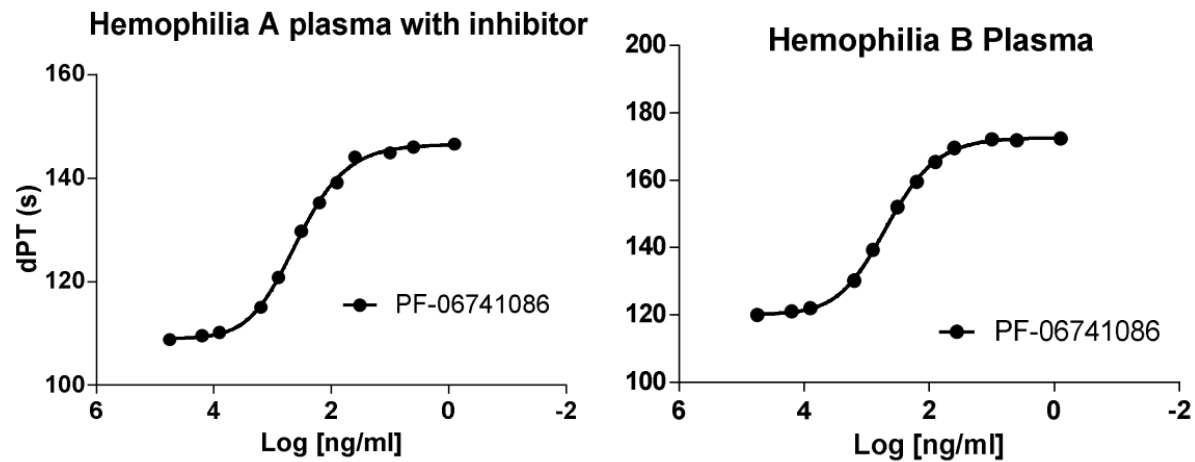
Source: Applicant Study #123404

Abbreviations: Ab, antibody; IgG1, immunoglobulin G1

The effect of marstacimab on hemostasis markers (dPT, thrombin generation assay [TGA] and aPTT) was also tested in plasma samples collected from patients with HA (citrate platelet-poor plasma) and HB (Study #135025) with poor coagulation factor activity. Marstacimab dose-dependently decreased dPT clotting times in all hemophilia plasma samples ([Figure 16](#) and [Figure 17](#)).

Figure 16. Dose-Dependent Marstacimab-Associated Changes in dPT (Seconds) in Platelet-Poor Plasma Samples Collected From Patients With Hemophilia A

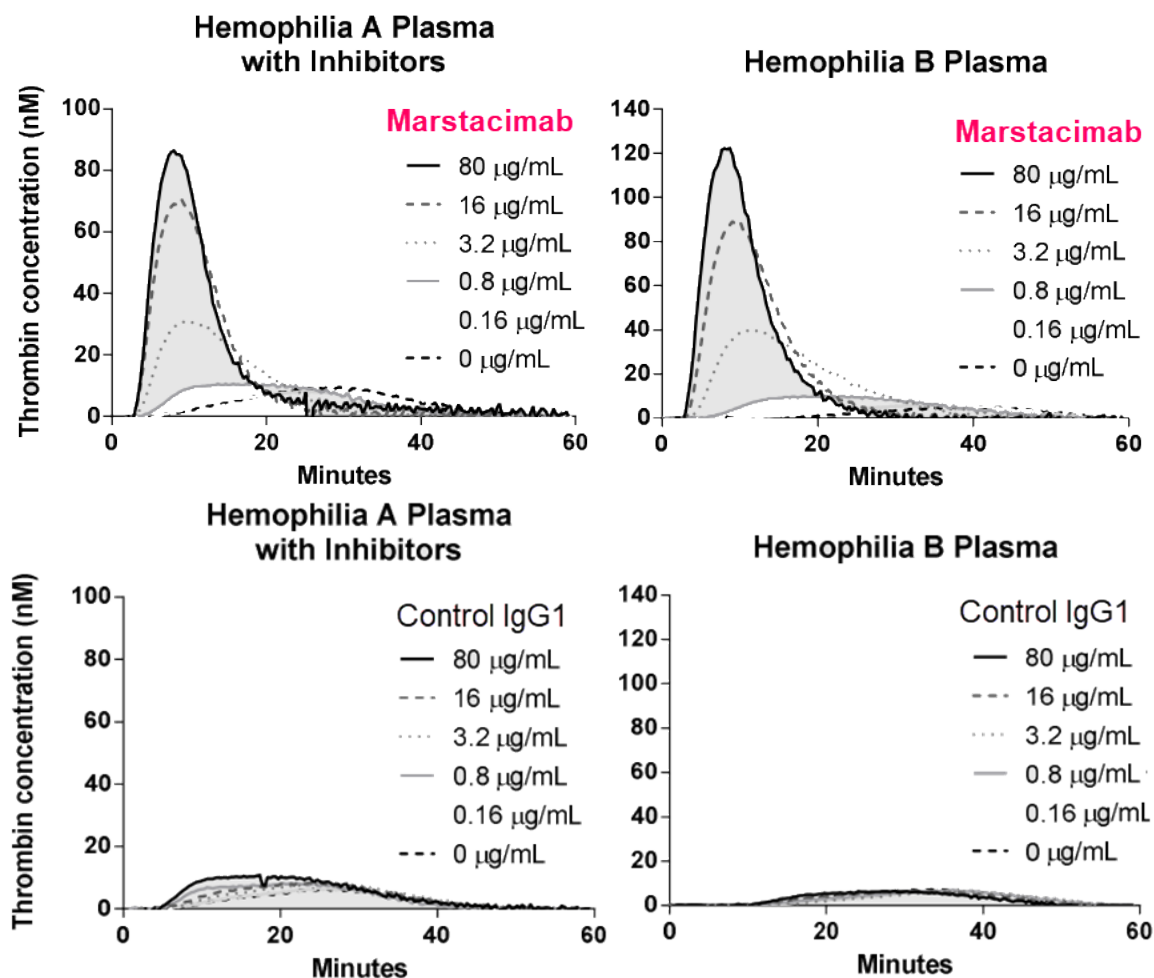
Source: Applicant provided Study #135025
Abbreviation: dPT, diluted prothrombin time

Figure 17. Dose-Dependent Marstacimab Associated Changes in dPT in Hemophilia A With Inhibitor and Hemophilia B Plasma

Source: Applicant-provided Study #135025
 Abbreviation: dPT, diluted prothrombin time

Consistent with the intended pharmacology, there was minimal change in aPTT (i.e., no change in this measure of the intrinsic pathway). Marstacimab restored thrombin in citrated platelet-poor HA with inhibitor or HB plasma ([Figure 18](#)). The findings suggest marstacimab may be capable of restoring thrombin in both hemophilia A and B patients. Marstacimab was also effective in generating thrombin compared to recombinant FVIIa (Eptacog alpha up to 20 µg/mL) and a combination (marstacimab+rFVII).

Figure 18. Marstacimab Effect on Thrombin Generation Assay (TGA) Time in Plasma From Hemophilia A (With Inhibitor) and Hemophilia B Humans



Source: Derived from Applicant Study #135025

Abbreviations: IgG1, immunoglobulin G1; TGA, thrombin generation assay time

Marstacimab alone or in combination with recombinant FVIIa (NovoSeven RT, eptacog alfa) produced comparable peak elevations in thrombin levels in platelet poor plasma from HA and HB donors ([Table 42](#)).

A marstacimab concentration of 16 $\mu\text{g/mL}$ produced peak thrombin levels comparable to levels to nonhemophilic plasma, which suggests that marstacimab may improve thrombin levels in patients with hemophilia A and B.

Table 42. Peak Thrombin Levels (nM) Following rFVIIa (2 pg/mL) Alone, Marstacimab (16 µg/mL) Alone and Marstacimab Plus rFVIIa in Hemophilia A and B Platelet-Poor Plasma and Nonhemophilia Plasma (Comparator)

Group	Vehicle (nM)	rFVIIa (nM)	Marstacimab (nM)	Marstacimab +rFVIIa (nM)	Nonhemophilic (nM)	Nonhemophilic Marstacimab (nM)
Hemophilia A	26-76	45-113	82-172	102-178	128-135	198
Hemophilia A with inhibitor	24-66	46-89	88-166	99-157	130-132	198-199
Hemophilia B	81	131	174	167	143	171

Source: Applicant Study #122443

Thrombin generation was measured in the presence of 1 pM tissue factor and 4µM phospholipid. The ranges of peak thrombin from each plasma type are depicted in the table.

Abbreviation: rFVIIa, recombinant factor VIIa

Marstacimab Activity In Vivo

The effectiveness of marstacimab was tested using in vivo models of HA (factor VIII deficient mice) and HB (Factor IX deficient mice). A laser induced injury was used to cremaster arteriolar endothelium to initiate injury (Study #135244 and #121321). The pharmacological effects of marstacimab on bleeding parameters (e.g., platelets, fibrin formation) were also assessed following laser injury in HA mice. Marstacimab decreased blood loss in both HA (76%) and HA (65%) mouse models. There were dose-dependent increases in coagulation in both HA and HB mouse models. Marstacimab increased platelet accumulation and fibrin generation in precapillary arterioles in HA mice. Marstacimab administered after onset of bleeding restored hemostasis within 2 minutes in the HB mouse tail clip injury model. Marstacimab's effect on reducing blood loss in this model lasted up to 192 hours ([Figure 4](#)).

13.1.2. Tabulated Summary of Individual In Vitro and In Vivo Pharmacology Studies Conducted With Marstacimab

Pharmacological activity of marstacimab was examined in hemophilia A and B mouse models. Marstacimab was effective in enhancing coagulation and bleeding in these models, supporting the proposed prophylactic benefits of marstacimab. The summaries of these studies are shown in [Table 43](#) and [Table 44](#).

Table 43. Tabulated In Vitro Pharmacology Studies With Marstacimab, PF-06741086

Study Number/Title/Methods	In Vitro Study Findings
PF-06741086_01Apr15_142056 Characterization of PF 06741086 in normal human whole blood using thromboelastography Method: In vitro dose-dependent TFPI neutralization examined by thromboelastography (TEG), clotting time (R) and clot formation time (K). Dose-dependent TFPI neutralization examined by TEG, clotting time (R) and clot formation time (K)	Marstacimab produced a dose-dependent decrease in clotting time (R) and clot formation time (K) compared to isotype control IgG1. No change in maximum amplitude, a measure of clot strength, was observed in the study.
PF-06741086_26Jul18_045123 Characterization of pf-06741086 activity in human hemophilia plasma in combination with activated prothrombin complex concentrate. Method: The study evaluated the effect of marstacimab in promoting coagulation in the thrombin generation assay (TGA) in combination with plasma derived activated prothrombin complex concentrate in platelet poor Ha plasma. aPCC (activated prothrombin complex, FEIBA™, FVIII inhibitor bypassing activity, 1 unit/mL) Marstacimab (PF-06741086, 16 µg/mL)	Dose-dependent changes in the TGA parameters, lag time and peak thrombin, were observed with the addition of either marstacimab or aPCC. A decrease in the lag time was observed with both marstacimab and aPCC (FEIBA) in hemophilia plasma. There was no additive decrease observed in the lag time when marstacimab was combined with FEIBA). The addition of marstacimab in combination with aPCC (FEIBA) to hemophilia plasma resulted in an increase in thrombin generation. PF-06741086 or aPCC (FEIBA) alone. However, this increase was within the reported range for nonhemophilic normal plasma.
15GR003 In vitro human C1q and FcR binding assays Method: PF-06741086 binding was tested by C1q binding ELISA and an FcR binding assay (CD16, CD32, and CD64) using ForteBio Octet RED's Bio-Layer Interferometry (BLI). Study was designed to test PF-06741086 binding potential for complement dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity activity. Control isotype IgG1 Fc (primary comparator): The study used an intact monoclonal 8.8 triple mutant [mAb 8.8 TM] that contains the same triple mutated IgG1 Fc portion but has no known binding specificity. Rituxan served as positive control.	Marstacimab does not bind to C1q, suggesting that it is unlikely to activate the classical complement pathway. Marstacimab binding to all FcγRs, was similar to, or lower than isotype control mAb 8.8 TM and lower than positive control. Marstacimab binding to all FcγRs, was lower than the positive control (IgG1- keyhole limpet hemocyanin). Conclusion: Marstacimab has low potential to elicit antibody-dependent cell-mediated cytotoxicity activity. Marstacimab was negative for C1q binding, suggesting it is unlikely to activate the classical complement pathway and cause complement dependent cytotoxicity.

HYMPAVZI (marstacimab-hncq) injection

Study Number/Title/Methods	In Vitro Study Findings
<u>15GR044</u> Pf-06741086 in vitro human cytokine release assay Method: To address the potential for marstacimab to cause cytokine release syndrome (CRS), an in vitro soluble phase (whole blood) cytokine release assay was carried out to determine whether PF-06741086 induced release of 3 human pro-inflammatory cytokines (TNF-α, IL-6, and IFN-γ). Whole blood from 8 healthy donors was tested for cytokine release following incubation with PF-06741086 PF-06741086=1, 10, 100 or 1000 μg/mL LPS=1 ng/mL Isotype control mAb 8.8 TM=1, 10, 100 or 1000 μg/ml	Marstacimab (F-06741086) did not elicit test article-related cytokine release of 3 human pro-inflammatory cytokines (TNF-α, IL-6, and IFN-γ) in the soluble phase assay.
<u>14MA087</u> A tissue cross-reactivity study of PF-06741086 in normal human, cynomolgus monkey, and Wistar-Han rat tissues Method: Study was designed to determine potential cross-reactivity of marstacimab with cryosections of human, cynomolgus monkey, and Wistar Han rats.	TFPI is predominantly synthesized in vascular endothelium as well as few other cells such as fibroblast and mononuclear cells and placenta. Therefore, as expected marstacimab binding was noted in endothelial cells one would expect release of TFPI (endothelial cell, placental spongiotrophoblasts, placental trophoblast, islet cells, endocrine epithelium, mesothelium). Monoclonal antibody binding to cytoplasmic sites generally not considered to have toxicological significance (ICH S6(R1)).

Source: Derived from Applicant's pharmacology studies

Abbreviations: aPCC, activated prothrombin complex; BLI, Bio-Layer Interferometry; CRS, dC1q, complement component 1q; CRS, cytokine release syndrome; ELISA, enzyme-linked immunosorbent assay; FEIBA, factor eight inhibitor bypassing activity; Fc, fragment crystallizable; FcR, Fc receptor; Fc γ R, Fc gamma receptor; FVIII, factor VIII; ICH, International Council for Harmonisation; IFN- γ , gamma interferon; IgG1, immunoglobulin G1; IL-6, interleukin 6; K, clot formation time; LPS, lipopolysaccharide; mAb, monoclonal antibody; R, clotting time; TEG, thromboelastography; TFPI, tissue factor pathway inhibitor; TGA, thrombin generation assay; TM, triple mutant.

Table 44. Tabulated In Vivo Pharmacology Studies With Marstacimab, PF-06741086

Study Number/Title/Methods	In Vivo Study Findings
16MA086 10-day intravenous investigative study of pf-06741086 and NovoSeven@RT in male Wistar Han rats Method: PF-06741086 50 mg/kg on Day 1, Day 8 NovoSeven@RT (rFVIIa) (0.4, 1, or 3 mg/kg QD, or 0.8 mg/kg (0.4 twice daily) on Days 8-10 alone or in combination with PF-06741086 (nonGLP)	Increased incidence and/or severity of microscopic minimal to mild, acute thrombi/emboli in lung and injection site (tail) were observed when marstacimab (50 mg/kg) administered with NovoSeven (3 mg/kg) Acute emboli were also observed with NovoSeven in the brain.

Table 45. Microscopic Findings in the Lungs of Male Wistar Han Rats

Group	1	2	3	6	9	10	11	12
PF-06741086 Dose (mg/kg)	0	50	0	0	0	50	0	50
Novoseven RT Dose (mg/kg)	0	0	0	3	0	3	0 (BID)	0.8 (0.4 BID)
Finding								
Lung ^a	5	5	5	5	5	5	5	5
Thrombi/emboli, acute								
Minimal (Grade 1)	0	1	2	2	1	2	2	1
Mild (Grade 2)	0	0	0	0	0	2	0	0
Injection Site (tail) ^a	5	5	5	5	5	5	5	5
Thrombi/emboli, acute								
Minimal (Grade 1)	0	1	1	1	0	4	0	1

Source: Study #16MA086

Abbreviation: BID, twice daily

The C_{max} and AUC for marstacimab and NovoSeven@RT were unaffected when combined.

19GR258 10-day subcutaneous (once weekly) or 3-day (twice daily) IV investigative study of PF-06741086 or factor VIII inhibitor bypassing activity (FEIBA) in male Wistar Han rats (non-GLP) Method: SC: PF-06741086 (30 mg/kg/day) on Day 1 and 8 and/or IV: FEIBA 10 (5 BID), 50 (25 BID) and 100 (50 BID) U/kg/day on Day 8-10	In a 10-day study conducted with marstacimab alone or in combination with FEIBA, marstacimab alone (30 mg/kg) increased (2-fold) thrombin-prothrombin complexes (TAT). FEIBA increase TAT and APTT but decreased PT time.
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Table 46. Coagulation and Hematology Parameters in FEIBA-Treated Rats

Dose (U/kg/day)	0	10 5 BID	50 (25 BID)	100 50 BID
APTT (sec)	15.32	-	1.26x	1.33x
PT (sec)	15.32	0.91x	0.77x	0.73x
TAT (µg/L)	2.98	1.55x	2.60x	4.53x
ALT (U/L)	22.4	-	-	1.97x

Source: Study #19GR258

Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin clotting time; BID, twice daily; PT, prothrombin time; TAT, thrombin-prothrombin complex

Marstacimab rats had no microscopic (i.e., lung emboli) findings in healthy rats.
FEIBA resulted in acute minimal to mild thrombi/emboli in the lungs in a dose dependent manner. Adding marstacimab to FEIBA treatment did not significantly alter the lung pathology produced by FEIBA.

HYMPAVZI (marstacimab-hncq) injection

Study Number/Title/Methods	In Vivo Study Findings																																																																																
<u>22GR075</u> 10-day subcutaneous (once weekly) or 3-day (twice daily) intravenous Investigative study of PF-06741086 or Byclot® in male Wistar Han rats (nonGLP) Method: Single or combination SC PF-06741086 (30 mg/kg/dose, once weekly) or single or combination IV of Byclot® (60, 120, or 180/120 µg/kg/day; 2 doses on Day 8 and 1 dose on Day 10)	Mean systemic exposure of marstacimab was not affected by FEIBA. Byclot alone shortened mean PT by 50% and prolonged APPT. Combination of marstacimab and Byclot appeared to have higher thrombin-antithrombin complex. Neither marstacimab nor Byclot had any adverse effect in the lung pathology. Table 47. Change in Hematology and Coagulation Parameters Relative to Control <table><tr><th rowspan="2">Parameter</th><th colspan="8">Males</th></tr><tr><th>PF-06741086 Control</th><th>Byclot Control</th><th>Byclot</th><th>Byclot</th><th>Byclot</th><th>PF-06741086 + Byclot</th><th>PF-06741086 + Byclot</th><th>PF-06741086 + Byclot</th></tr><tr><td>Dose^a</td><td>0</td><td>0</td><td>60</td><td>120</td><td>180/120</td><td>30 + 60</td><td>30 + 120</td><td>30 + 180/120</td></tr><tr><td>PT Rat (sec)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>D10</td><td>12.56</td><td>12.50</td><td>0.50x</td><td>0.47x</td><td>0.45x</td><td>0.52x</td><td>0.51x</td><td>0.50x</td></tr><tr><td>APTT (sec)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>D10</td><td>15.76</td><td>15.13</td><td>1.35x</td><td>1.42x</td><td>1.51x</td><td>1.44x</td><td>1.46x</td><td>1.45x</td></tr><tr><td>TAT Complex (µg/L)</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>D10</td><td>4.08</td><td>5.10</td><td>-</td><td>-</td><td>-</td><td>1.89x</td><td>1.50x</td><td>1.41x</td></tr></table> Source: Study #22GR075 Abbreviations: APTT, activated partial thromboplastin clotting time; PT, prothrombin time; TAT, thrombin-prothrombin complex	Parameter	Males								PF-06741086 Control	Byclot Control	Byclot	Byclot	Byclot	PF-06741086 + Byclot	PF-06741086 + Byclot	PF-06741086 + Byclot	Dose ^a	0	0	60	120	180/120	30 + 60	30 + 120	30 + 180/120	PT Rat (sec)									D10	12.56	12.50	0.50x	0.47x	0.45x	0.52x	0.51x	0.50x	APTT (sec)									D10	15.76	15.13	1.35x	1.42x	1.51x	1.44x	1.46x	1.45x	TAT Complex (µg/L)									D10	4.08	5.10	-	-	-	1.89x	1.50x	1.41x
Parameter	Males																																																																																
	PF-06741086 Control	Byclot Control	Byclot	Byclot	Byclot	PF-06741086 + Byclot	PF-06741086 + Byclot	PF-06741086 + Byclot																																																																									
Dose ^a	0	0	60	120	180/120	30 + 60	30 + 120	30 + 180/120																																																																									
PT Rat (sec)																																																																																	
D10	12.56	12.50	0.50x	0.47x	0.45x	0.52x	0.51x	0.50x																																																																									
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D10	15.76	15.13	1.35x	1.42x	1.51x	1.44x	1.46x	1.45x																																																																									
TAT Complex (µg/L)																																																																																	
D10	4.08	5.10	-	-	-	1.89x	1.50x	1.41x																																																																									
<u>1001043</u> Characterization of pharmacokinetics, pharmacodynamics of PF-06741086 after intravenous and subcutaneous doses to male Cynomolgus monkeys Method: Marstacimab IV: 1, 3 & 1 mg/kg/wk, Marstacimab IV/SC: 10, 10 & 3 mg/kg/wk Marstacimab IV/SC: 1, 3 & 1 mg/kg/wk	Mean systemic exposures of marstacimab was not affected by Byclot. Marstacimab clearance appeared to follow a target TMDD which is characterized by dose-dependent PK and drug-dependent target turnover. T _{1/2} increased from ~12 hr at 1 mg/kg IV to ~40 hr at 3 mg/kg IV and 36 hr at 3 mg/kg SC to 150 hr at 10 mg/kg IV & 162hr at 10 mg/kg SC. Plasma TFPI concentrations increased with increase in marstacimab dose between 24 and 240 hr. (48 ng/mL at 0 time to up to 973 ng/mL). Marstacimab decreased diluted PT clotting time. Change in dPT and clotting time were stable from 24 to 240 hr.																																																																																

HYMPAVZI (marstacimab-hncq) injection

Study Number/Title/Methods	In Vivo Study Findings																														
<u>18GR090</u> 3-day intravenous investigative study of factor eight inhibitor bypassing activity (FEIBA) in male Wistar Han rats testing facility Method: FEIBA (factor VIII) inhibitor bypassing activity: Rats were dosed for 3 days with 50 (25 BID), 100 (50 BID) or 200 (100 BID) intravenous doses of FEIBA.	Intravenous FEIBA (factor VIII inhibitor bypassing activity) was well tolerated. Prothrombin time (PT) tended to be lower at 50 U/kg/d by Day 3 but normalized by Day 4. APTT was prolonged but normalized by Day 4. Fibrinogen was higher by Day 3.																														
Table 48. Changes in PT in FEIBA-Treated Rats																															
<table><tr><th>Parameter</th><th></th><th colspan="3">Dose (U/kg/day)</th></tr><tr><td></td><td>0</td><td>50 25 (BID)</td><td>100 50 (BID)</td><td>200 (100 BID)</td></tr><tr><td>PT (sec)</td><td colspan="4"></td></tr><tr><td>5PID</td><td>13.90</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Day 3</td><td>13.60</td><td>0.77x</td><td>0.72x</td><td>*0.70x</td></tr><tr><td>Day 4</td><td>13.78</td><td>-</td><td>-</td><td>-</td></tr></table>		Parameter		Dose (U/kg/day)				0	50 25 (BID)	100 50 (BID)	200 (100 BID)	PT (sec)					5PID	13.90	-	-	-	Day 3	13.60	0.77x	0.72x	*0.70x	Day 4	13.78	-	-	-
Parameter		Dose (U/kg/day)																													
	0	50 25 (BID)	100 50 (BID)	200 (100 BID)																											
PT (sec)																															
5PID	13.90	-	-	-																											
Day 3	13.60	0.77x	0.72x	*0.70x																											
Day 4	13.78	-	-	-																											
Source: Study #18GR090 Abbreviations: 5PID, 5 days prior to initiation day; BID, twice daily; PT, prothrombin time																															
At ≥100 (50 BID) U/kg/day, FEIBA related microscopic findings, included increased incidence and/or severity of thrombi/emboli (acute and/or organizing) in the lung and injection site (tail).																															
Other microscopic changes (hemorrhage, congestion, edema, increased incidence of mild mixed cell infiltration, inflammation/degeneration/necrosis in muscle tissue, acanthosis, and intra/subepidermal vacuole/pustule/cleft) at the injection site (tail) were considered secondary to thrombi/emboli resulting in circulatory compromise.																															

Source: Derived from Applicant's pharmacology studies

Abbreviations: 5PID =5 days prior to initiation day; APTT, activated partial thromboplastin time; AUC, area under the concentration-time curve; BID, twice daily; dPT, diluted prothrombin time; FEIBA, factor eight inhibitor bypassing activity; GLP, Good Laboratory Practice; IV, intravenous; PK, pharmacokinetics; PT, prothrombin time; QD, once daily; rFVIIa, recombinant factor VIIa; SC, subcutaneously; T_{1/2}, elimination half-life; TAT, thrombin-prothrombin complex; TFPI, tissue factor pathway inhibitor; TMDD, target-mediated drug disposition

13.1.2.1. Safety Pharmacology

Safety pharmacology assessments were incorporated into the 3-month toxicology study in monkeys ([Table 49](#)). Intravenous administration of marstacimab at doses ranging from 30 to 500 mg/kg/week and SC administration of 90 mg/kg/week to monkeys had no effect on respiratory, neurological, or cardiovascular parameters. There was no change in QTc interval following intravenous administration of 500 mg/kg/week marstacimab in monkeys.

Table 49. Safety Pharmacology Studies

Study Features and Methods	Details
Study title	A 3-Month Intravenous or Subcutaneous Injection Toxicity and Toxicokinetic Study of PF-06741086 in Cynomolgus Monkeys with a 6-Week Recovery Phase (Study #20062114)
Species/strain	Cynomolgus Monkeys
Number/sex/group	3-5 per sex/group
Dosage mg/kg/week	IV: 30, 90 or 500 mg/kg/week
	SC: 90 mg/kg/week
Findings	Weekly intravenous and SC administration of PF-06741086 had no effect on cardiovascular, (QT interval, blood pressure, heart rate), respiratory rate or neurological parameters.

Source: Applicant provided Study #20062114

Abbreviations: IV, intravenously; No., number; SC, subcutaneously

13.1.2.1.1. ADME / Pharmacokinetics

The pharmacokinetics (PK) and toxicokinetics (TK) of marstacimab were characterized following once weekly subcutaneous and intravenous administrations in both Wistar Han rats and cynomolgus monkeys. Single and repeat dose PK (Study #13MA070, 8299672) and repeat dose TK studies (Studies #20064198, #20062114, #20089324) showed marstacimab exposure increased with increases in dose in both rats and monkeys. Importantly, marstacimab is cleared by target-mediated drug disposition. Low doses are rapidly cleared by target, while higher doses saturate target-mediated clearance, leading increasing half-life ($t_{1/2}$). The $t_{1/2}$ for marstacimab at 1 mg/kg intravenous (IV) was 12.3 hours in cynomolgus monkeys but was extended to 118 hours at 10 mg/kg IV ([Table 50](#) and [Table 51](#)). The volume of distribution (Vd) in the monkey was estimated to be 34 to 65 mL/kg, which is similar the Vd of other monoclonal antibodies.

Table 50. Pharmacokinetic Parameters on Day 1 After Single IV Dose of Marstacimab in Rats and Monkeys

Species	Dose, mg/kg	AUC, ng·h/mL ¹	CL, mL/h/kg	V _{ss} , mL/kg	T _{1/2} , h
Rat ² (Study #13MA067)	3	2,810,000	0.977	43.9	37.8
	30	29,700,000	0.893	43.8	45.1
	90	111,000,000	0.667	42.2	42.9
Monkey, (Study #13MA070)	3	3,510,000	0.606	34.1	—
	30	34,700,000	0.314	65.1	—
	90	138,000,000	0.248	51.8	—

HYMPAVZI (marstacimab-hncq) injection

Species	Dose, mg/kg	AUC, ng·h/mL ¹	CL, mL/h/kg	V _{ss} , mL/kg	T _{1/2} , h
Monkey ²	1	386,000	2.61	—	12.3
(Study #8299672)	10	14,100,000	0.508	—	118

Source: Applicant provided Studies #13MA067, #13MA070, and #8299672

¹ The AUC values for studies 13MA067, 13MA070, and 8299672 were AUC96, AUC96, and AUC168, respectively.

² Day 8 marstacimab plasma concentrations from the exploratory toxicity studies, and Day 8 TK parameters from the PK/PD data are presented in study reports.

“—” indicates unable to determine

Abbreviations: AUC, area under the concentration-time curve; CL, clearance; IV, intravenous;

PK/PD, pharmacokinetic/pharmacodynamic; T_{1/2}, elimination half-life; TK, toxicokinetic; V_{ss}, volume of distribution at steady-state

Administration of marstacimab in combination with other compounds had no impact on marstacimab levels in rats suggesting drug-drug interaction is highly unlikely. No specific metabolism, protein binding, or excretion studies were conducted in nonclinical species. Marstacimab is not expected to bind to albumin or α -1 acid glycoprotein. Marstacimab is predicted to be metabolized by a proteomic catabolism. Clearance of marstacimab follows a target-mediated drug disposition (TMDD), which predicts that higher affinity will result in higher clearance. Since marstacimab has lower affinity to TFPI than concizumab, larger doses should be necessary to produce a similar pharmacodynamic (PD) effect as concizumab. TMDD theory also predicts that lower doses will be cleared more rapidly while larger saturating doses will lead to a longer half-life. The low potency of marstacimab relative to concizumab (7-fold lower) thus requires a larger dose to achieve therapeutic efficacy, which results in a longer half-life that allows less frequent dosing of marstacimab in both nonclinical species (once weekly) and humans (once weekly mg) compared to concizumab.

Table 51. Pharmacokinetics of Marstacimab Following Single SC and IV Administration to Rat and Monkey

Mean PK Parameters	Rat				20 mM His, 8.5% sucrose, pH 5.8	
Dose (mg/kg)	3 (SC)	3 (IV)	30 (IV)	90 (IV)		
C _{max} (ng/mL)	27,000	88,500	882,000	34,800,000		
T _{max} (h)	72	0.083	0.083	0.083		
AUC ₉₆	1,960,000	2,810,000	29,700,000	111,000,000		
CL (mL/h/kg)	--	0.977	0.893	0.667		
V _{ss} (mL/kg)	--	43.9	43.8	42.2		
t _{1/2} (h)	--	37.8	45.1 ^b	42.9 ^b		

Mean PK Parameters ^b	Cynomolgus Monkey		20 mM His, 8.5% sucrose, pH 5.8			
Dose (mg/kg)	3 (SC)	3 (IV)	30 (IV)	90 (IV)	1 (IV)	10 (IV)
C _{max} (ng/mL)	7140	127,000	582,000	2,680,000	20,400	289,000
T _{max} (h)	37	48	0.0	0.0	0.083	0.083
AUC ₉₆ or AUC ₁₆₈ (ng·h/mL) ^c	432,000	3,510,000	34,700,000	38,000,000	386,000	14,100,000
CL (mL/h/kg)	--	0.606	0.314	0.248	2.61	0.508
V _{ss} (mL/kg)	422	34.1	65.1	51.8	--	--
t _{1/2} (h)	--	--	--	--	12.3	118 ^b

Source: Applicant provided rat Study #13MA067 and monkey Studies #13MA070 & #829967

^a Single-dose PK was calculated after the first dose in the exploratory toxicity study or the PK/PD study. Day 8 PF-06741086 plasma concentrations or Day 8 TK parameters are presented in the individual study reports.

^b Sampling intervals may not have been sufficient to properly calculate or characterize t_{1/2}.

Abbreviations: AUC₉₆, area under the concentration-time curve at 96 hours; CL, clearance; C_{max}, maximum concentration; his, histidine; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; t_{1/2}, elimination half-life; TK, toxicokinetic; T_{max}, time to maximum concentration; V_{ss}, volume at steady-state

13.1.2.2. Toxicokinetic Parameters

TK parameters with administration of marstacimab by the SC and IV routes to Wistar Han rats and Cynomolgus monkey are shown in [Table 52](#), [Table 53](#), and [Table 54](#).

Plasma levels of marstacimab in nonclinical species were measured using a validated biotin-labeled mouse anti-marstacimab monoclonal antibody on streptavidin coated microtiter plate and detected using a ruthenium-labeled mouse anti-human IgG Fc antibody. Analysis of plasma samples for antidrug antibody (ADA) detected ADA in a minority of rats (~28%) in the 3-month study found no evidence of marstacimab neutralization ([Table 52](#)). There was no evidence of ADA in the 3-month monkey or 6-month rat studies. Marstacimab's systemic exposure increased with dose in a slightly greater than dose-proportional manner on Days 29 and 85 in the 3-month rat study but in a dose-proportional manner in the 3-month monkey and 6-month rat studies. There were no sex-related differences in drug exposures in rats or monkeys. Following repeated SC dosing of marstacimab, time to maximum plasma concentration (T_{max}) ranged between 48 to 63 hours in rats and from 41 to 64 hours in monkeys.

Table 52. Toxicokinetic Parameters of Marstacimab in the 3-Month Rat Study Following IV and SC Routes of Administration

Dose (mg/kg/dose)	Day	C_{max} , $\mu\text{g/mL}$	AUC_{0-168h} , $\mu\text{g}\cdot\text{hours/mL}$	AUC_{0-168h}/Dose , $\mu\text{g}\cdot\text{hours/mL/mg/kg}$
60 (IV)	1	1430±109	62200±14000	1040±233
	29	1670±339	57700±14800	962±247
	85	1530±327	54500±19200	908±320
180 (IV)	1	3690±965	205000±45800	1140±254
	29	6190±1930	263000±27300	1460±152
	85	5410±456	283000±19300	1570±107
180 (SC)	1	693±199	74800±23000	416±128
	29	524±236	57100±35000	317±194
	85	416±170	45600±22400	253±124
1000 (IV)	1	21000±6630	1180000±227000	1180±227
	29	28900±2480	1770000±124000	1770±124
	85	27800±3220	1940000±236000	1940±236

Source: Applicant Study #20064198 (14MA086)

Abbreviations: AUC_{0-168h} , area under the concentration-time curve from time 0 to 168 hours; C_{max} , maximum concentration; IV, intravenous; SC, subcutaneous

Table 53. Pharmacokinetic Parameters of Marstacimab in 3-Month Monkey Study Following IV and SC Routes Administration

Dose (mg/kg/dose)	Day	T_{max} , h	C_{max} , $\mu\text{g/mL}$	AUC_{0-168h} , $\mu\text{g}\cdot\text{h/mL}$
30 (IV)	1	0.25±0.0	817±107	55,700±4500
	29	2.2±3.0	1240±81.7	139,000±18200
	85	8.2±12	1290±233	160,000±38800
90 (IV)	1	5.2±9.5	1570±136	173,000±10300
	29	6.1±9.2	3600±225	387,000±31400
	85	1.2±2.3	4510±471	474,000±71800
90 (SC)	1	64±20	969±83.5	123,000±11100
	29	41±17	2160±141	315,000±22600
	85	48±0.0	2480±361	364,000±66600

HYMPAVZI (marstacimab-hncq) injection

Dose (mg/kg/dose)	Day	T _{max} , h	C _{max} , µg/mL	AUC _{0-168h} , µg•h/mL
500 (IV)	1	2.0±2.8	10500±1130	937,000±84200
	29	1.4±2.4	17300±1440	1,820,000±177000
	85	0.83±1.8	18400±1100	2,000,000±168000

Source: Applicant provided PK data, Study #20062114 (14MA097)

Abbreviations: AUC_{0-168h}, area under the concentration-time curve from time 0 to 168 hours; C_{max}, maximum concentration; IV, intravenous; SC, subcutaneous; T_{max}, time to peak concentration

Table 54. Toxicokinetic Parameters of Marstacimab in 6-Month Rat Following IV Route of Administration

Dose, mg/kg/dose ^{1,2}	Day	T _{max} , h	C _{max} , µg/mL	AUC _{0-168h} , µg•h/mL
60	1	0.17±0.0	1640±34	68700±9 550
	120	0.90±0.73	2020±110	62000±3630
	176	0.17±0.0	2330±142	73100±5490
	183	0.17±0.0	2130±149	69700±7750
180	1	3.1±3.0	5170±758	239000±29600
	120	3.1±3.0	5820±362	354000±59500
	176	0.90±0.73	7030±547	373000±55100
1000	1	0.17±0.0	23300±2030	1120000±82700
	120	3.9±3.0	27100±2700	1740000±161000
	176	4.6±2.9	29800±2610	1840000±189000

Source: Applicant Study #20089324 (15MA123)

¹ 4 animals/sex/dose group with serial sampling except for Day 1 for the 60 mg/kg/dose group where the number of males was 3 and females 4 and Day 1 for the 1000 mg/kg/dose group where n=3/sex.

² Animals were dosed on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, 92, 99, 106, 113, 120, 127, 134, 141, 148, 155, 162, 169, 176, and 183.

Abbreviations: AUC_{0-168h}, area under the concentration-time curve from time 0 to 168 hours; C_{max}, maximum concentration; IV, intravenous; T_{max}, time to peak concentration

13.1.2.2.1. General Toxicology

Marstacimab produced a clear pharmacodynamic response in mouse hemophilia models. While marstacimab increased D-dimer, a marker of blood clot formation, in healthy rats and monkeys, administration of marstacimab did not decrease prothrombin time, APTT, or increase fibrin. No histopathological evidence of bleeding was observed at 200-times the area under the concentration-time curve (AUC) at the maximum recommended human dose (MRHD) in the 3-month rat study (doses up to 1000 mg/kg/week) or 3-month monkey study (doses up to 500 mg/kg/week). However, minimal acute emboli were detected in the 6-month rat study in the lung at 60 (1F, 1M), 180 (4F, 2M) and 1000 mg/kg/week (1F, 0M) doses and in tail injection sites at 180 (2F, 1M) and 1000 mg/kg/week (2F, 1M). Neither the lung nor the tail injection site thrombi/emboli findings in the 6-month rat study were considered adverse based on (a) absence of secondary lung tissue injury, (b) lack of clear dose-response, and (c) absence of change in prothrombin time, a marker of extrinsic and common pathway integrity. Similar acute minimal incidences of lung emboli were observed at the low dose of 30 mg/kg/week in one monkey (3-month study) and in one male rat (pharmacology study) at 50 mg/kg. In none of the cases was there any evidence of secondary lung injury, suggesting the lung emboli likely occurred at a very low level or at the study termination, possibly due to combined effect of marstacimab plus stress (exsanguination). Despite the unclear relationship between lung emboli in healthy animals and marstacimab, the anticipated risk of thrombi/emboli in hemophilia patients cannot be dismissed.

HYMPAVZI (marstacimab-hncq) injection

In summary, the presence of marstacimab-related acute minimal lung and tail thrombi/emboli identified sporadically across studies, suggests that marstacimab contributes to a minimally pro-coagulatory state in healthy animals that remains in homeostasis under most conditions. Thus, the top weekly intravenous dose of 1000 mg/kg/dose in rats and 500 mg/kg/dose in monkeys were regarded as the no observed adverse effect level (NOAEL) doses, with AUC exposures approximately 200-times greater than clinical exposure at the maximum recommended human dose ([Table 55](#)).

Table 55. Exposure Multiples Provided by Nonclinical Toxicology Studies Based on AUC

Toxicology Study	Route	Sex	NOAEL ¹ (mg/kg/week)	AUC _{168h} (µg*hr/mL)	Exposure Multiples Based on AUC _{168h}
3-month rat	IV	M+F	1000	1,940,000	212
	SC	M+F	180	45,600	5
6-month rat	IV	M+F	1000	1,840,000	201
3-month monkey	IV	M+F	500	2,000,000	219
	SC	M+F	90	364,000	40
Fertility & embryofetal develop (FEED) ³	IV	M	1000	1,940,000	212 ²
Maximum recommended human dose, 300 mg ⁴				9,146	

Source: Reviewer generated table

¹ NOAEL values represent marstacimab doses injected intravenously once a week.

² The exposure multiples for the fertility and embryofetal development study was based on AUC from the 3-month rat toxicology study.

³ FEED study was conducted in males (total 11 doses), mated with naïve female rats.

⁴ Steady state clinical AUC at the MRHD (maximum recommended human dose) of 300 mg was 9146 µg.h/mL. The current recommended clinical dose is 300 mg loading SC dose followed by weekly 150 mg SC dose.

Abbreviations: AUC, area under the concentration-time curve; AUC_{168h}, area under the concentration-time curve at 168 hours; FEED, fertility and embryofetal development; IV, intravenous; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; SC, subcutaneous

Study #20064198 / Title: A 3-Month Intravenous or Subcutaneous Injection Toxicity and Toxicokinetic Study of PF-06741086 in Rats With a 6-Week Recovery Phase

Key Study Findings

- Minimal, nondose dependent decreases in prothrombin time, with an unexpected prolongation of APTT, and lower fibrin concentrations, were observed during the study but not at the end of the recovery.
- Marstacimab was not associated any adverse histopathology findings in rats at SC doses up to 180 mg/kg/week or IV doses up to 1000 mg/kg/wk.
- ADAs were detected in 9/32 (28.1%) treated animals but had no impact on marstacimab exposure.
- With no marstacimab related adverse findings, the highest 1000 mg/kg/week IV and 180 mg/kg/week SC doses were accepted as the NOAELs in the 3-month rat study. Exposure at the SC NOAEL dose were 5-times the exposure at the MRHD on an AUC basis.

Study #20062114 / Title: A 3-Month Intravenous or Subcutaneous Injection Toxicity and Toxicokinetic Study of PF-06741086 in Cynomolgus Monkeys With a 6-Week Recovery Phase

Key Study Findings

- Contrary to expected pharmacodynamic effect of marstacimab, there was an increase in prothrombin time and aPTT and decrease in fibrinogen concentration (FIB) concentrations (~60%). There was, however, a significant increase in D-dimer concentration (DDIM) (marker of blood clot) that supported pharmacological activity.
- There was a single minimal acute incidence of lung emboli at low dose of 30 mg/kg/week IV.
- There were no detectable ADAs in marstacimab treated monkeys given by IV or SC route.
- The highest doses of 500 mg/kg/wk IV and 90 mg/kg/week SC were considered the NOAEL doses. Exposures at the IV NOAEL were approximately 219X the exposure at the MRHD dose on an AUC basis. Exposures at the highest SC dose of 90 mg/kg were roughly 40X the exposure at the MRHD on an AUC basis.

Study #20089324 / Title: A 6-Month Intravenous Bolus Injection Toxicity Study of PF-06741086 in Rats With a 6-Week Recovery Period

Key Study Findings

- Contrary to expected pharmacodynamic effect, marstacimab increased prothrombin time at HD of 1000 mg/kg/week in both sexes and increased APTT (all doses) and decreased FIB (all doses). DDIM levels, a marker of increase in risk of blood-clot formation was increased at all doses.
- Minimal acute thrombi/emboli with no secondary tissue injury was observed in the lungs and tail vein injection sites at ≥ 60 mg/kg/week.
- In contrast to the results of the 3-month rat study, there were no detectable ADAs in the 6-month rat study. Based on the minimal emboli being considered non-adverse, the highest IV dose of 1000 mg/kg/week was considered the NOAEL in rats (approximately 200X the exposure at the MRHD on an AUC basis).

13.1.2.2.2. Genetic Toxicology

As a monoclonal antibody, genotoxicity assessment of marstacimab was not scientifically appropriate and therefore was not conducted.

13.1.2.2.3. Carcinogenicity

As a biological compound, the genotoxicity of marstacimab was evaluated based on a weight of evidence (WoE) approach, the key points of which are highlighted below:

- Biological nature of marstacimab: Biologicals possess no inherent carcinogenic risk based on chemical structure or metabolism.
- Mechanism of action/therapeutic target: Marstacimab is an inhibitor of TFPI, a blood clotting regulator with no identified role in carcinogenic pathways.
- Toxicology data: No preneoplastic lesions, evidence of hormonal perturbation, or signs of immune modulation were observed across studies in animals.

Based on the WoE provided by the Applicant, the Division agreed that marstacimab is unlikely to pose a significant carcinogenicity safety concern for humans and therefore considered a 2-year study in rats unlikely to provide additional useful information.

13.1.2.2.4. Reproductive Toxicology

Study #00655204 / Title: A Fertility and Early Embryonic Development Study of PF-06741086 by Intravenous Injection in Male Wistar Rats

Key Study Findings

- Males Wistar rats dosed intravenously once weekly with marstacimab up to 1000 mg/kg (total of 11 doses) showed no adverse effects on fertility.
- Marstacimab treatment in males mated with treatment-naïve females did not affect pregnancy, implantation, or embryonic survival.
- The highest once weekly dose of 1000 mg/kg marstacimab was accepted as the NOAEL. Although drug exposures were not determined, plasma concentrations of marstacimab measured at 5 minutes postdose supported a determination of adequate drug exposure, because values were consistent with existing TK data. Based on existing AUC data, exposure at the NOAEL in the study was likely 201-times the exposure at the MRHD of 300 mg per week on an AUC basis.

HYMPAVZI (marstacimab-hncq) injection

Table 56. Rat Local Tolerance Study With Marstacimab

Study Features and Methods	Details
Study title	One-day subcutaneous injection local tolerance study of pf-06741086 in Wistar Han rats with a one-week recovery (No.16GR324)
Species/Strain/Method	Wistar Han Rats, GLP Study
Method	Rats (15/sex/dose) were injected with single SC dose of 0 or 300 mg/kg marstacimab
Study findings	Marstacimab (300 mg/kg): Reversible minimal to mild increase in mixed cell infiltration (macrophages, neutrophile, lymphocytes & plasma cells) at injection site; minimal edema and/or hemorrhage in dermis. Decrease in food consumption (0.90x control). NOAEL AUC_{168h} = 139,000 µg•hr/mL was about 15X the MRHD of 300 mg on AUC_{168h} basis Subcutaneous administration of marstacimab produced a reversible in mixed cell infiltration at the inject sites

Source: Applicant derived data (Study #16GR324)

Abbreviations: AUC_{168h}, area under the concentration-time curve at 168 hours; GLP, Good Laboratory Practice; MRHD, maximum recommended human dose; No., number; NOAEL, no observed adverse effect level; SC, subcutaneous**Impurities/Degradants**

As a biological compound, marstacimab impurities consisted of process-related impurities, product-related impurities, and potential contaminant in the drug substance. Process-related impurities originated from manufacturing process which consisted of host cell proteins, host cell DNA and cell culture media components and impurities related to downstream processing of marstacimab. The residual DNA impurities were DNA fragments (CHO cell line), cell culture media (b) (4) (chromatography purification (b) (4)) and contaminants (endotoxin, bioburden, mycoplasma, viruses). These impurities were at very low levels, not greater than the quantification limit for all except for host cell protein. [Table 57](#) lists the process-related impurities evaluated for marstacimab.

Table 57. Marstacimab Process-Related Impurities

Impurity	Source
Residual DNA	CHO cell line
Host cell proteins (HCP)	CHO cell line
(b) (4)	Cell culture media
	Cell culture media (b) (4)
	Cell culture media
	Cell culture media
	(b) (4)

Source: Applicant data

Abbreviations: CHO, Chinese hamster ovary; HCP, host cell proteins; (b) (4)

HYMPAVZI (marstacimab-hncq) injection

- Marstacimab batches used in toxicology studies contained similar or lower levels of impurities compared to the clinical batches. Safety of process-related impurities was therefore addressed in toxicology studies.
- The process-related residual DNA content/impurities detected in (b) (4) (commercial manufacturing process) of process performance qualification (PPQ) were less (b) (4) pg/mg.
- The host cell protein content in process (b) (4) batches were no more than (b) (4) ng/mg, the limit of quantification of LC/MS/MS.
- (b) (4) leaching from the chromatography column in the process (b) (4) was no more than (b) (4) ng/mg, the quantitation limit.

Overall, impurities were qualified and within the marstacimab drug substance specifications. Since the commercial manufacturing process (b) (4) batches had lower impurities than those tested in nonclinical studies, the safety of the impurities is adequately addressed, and no safety concern was identified.

Excipients in Drug Product

Marstacimab is an IgG1 lambda human mAb with two identical heavy chains and two identical light chains, covalently linked with four inter-chain disulfide bonds. To be marketed marstacimab is a sterile, preservative free and colorless drug product (150 mg/mL, pH 5.8) formulated for subcutaneous injection in a 1 mL prefilled single dose disposable glass (Type I (b) (4) glass) syringe pen with a 27-gauge thin walled 1/2-inch needle with a chlorobutyl elastomer plunger stopper.

Excipients used in marstacimab clinical formulation are all generally regarded as safe (L-histidine and L-histidine monohydrochloride, sucrose, disodium edetate, polysorbate 80 ([Table 58](#))). Marstacimab is sensitive to light therefore susceptible to photodegradation. All excipients had been used at similar or higher concentrations with other injectables ([Table 59](#)).

Table 58. Composition of Marstacimab Drug Product

Name of Ingredients	Reference to Standard	Function	Unit Formula (mg/mL)
Marstacimab	In-house specification	Active ingredient	150
L-histidine ¹	USP, Ph. Eur., JP	(b) (4)	1.12 ²
L-histidine monohydrochloride ³	Ph. Eur., JP		2.67 ²
Sucrose	Ph Eur., NF, JP		85
Disodium edetate ⁴	USP, Ph. Eur., JP		0.05
Polysorbate 80	Ph Eur., NF, JP		0.2
Water for injection	USP, Ph. Eur., JP		q.s. to 1 mL

Source: Applicant provided data

¹ Also referred to as histidine.

² The combination of L-histidine and L-histidine monohydrochloride is equivalent to 20 mM histidine

³ Also referred to as L-histidine monohydrochloride monohydrate, histidine monohydrochloride, L histidine hydrochloride hydrate, and L-histidine hydrochloride monohydrate.

⁴ Also referred to as edetate disodium dihydrate, edetate disodium, disodium edetate hydrate, and EDTA

Abbreviations: JP, Japanese Pharmacopeia; NF, National Formulary; Ph Eur, European Pharmacopeia; q.s., quantum satis (quantity to satisfy); USP, United States Pharmacopeia

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HYMPAVZI (marstacimab-hncq) injection

Table 59. Batch Analysis for Marstacimab Drug Substance Process 1

(b) (4)



Table 60. Marstacimab Drug Substance Specification

Quality Attribute		Analytical Procedure	Acceptance Criteria Release and Shelf Life
Characteristics			
Appearance (Clarity)		Ph. Eur. 2.2.1 and JP 2.61	(b) (4)
Appearance (Coloration)		Ph. Eur. 2.2.2 and JP 2.65	
pH		USP <791>, Ph. Eur. 2.2.3, and JP 2.54	
Protein Concentration		UV Spectroscopy	
Charge Heterogeneity	Acidic Species	iCE	
	Main Species		
	Basic Species		
Identity			
Peptide Profile ^{a, b}		Peptide Map	Comparable to Reference Material
Purity			
Monomer		SE-HPLC	(b) (4)
Heavy Chain and Light Chain		CGE (Reducing)	
Intact IgG		CGE (Non-reducing)	
Product Related Impurities			
HMMS		SE-HPLC	(b) (4)
Fragments		CGE (Reducing)	
Biological Activity			
Potency / Biological Activity		Inhibition Assay	Relative Potency (b) (4)
Process Related Impurities			
HCP ^b		HCP ELISA	(b) (4)
Safety			
Bioburden		USP <61>, Ph. Eur 2.6.12, and JP 4.05	(b) (4) CFU/30 mL
Endotoxin ^c		USP <85>, Ph. Eur 2.6.14, and JP 4.01	(b) (4) EU/mL

Source: Applicant-provided data table

^a Quantitative criteria defining the acceptance criterion^b Release test only^c Acceptance criterion equivalent to ≤0.25 EU/mg based on the target protein concentration for DP

Abbreviations: B, brown; CFU, colony forming units; CGE, capillary gel electrophoresis; DP, drug product; ELISA, enzyme-linked immunosorbent assay; EU, endotoxin units; HCP, host cell protein; HMMS, high molecular mass species; iCE, imaged capillary isoelectric focusing; IgG, immunoglobulin G; JP, Japanese Pharmacopeia; NF, National Formulary; NTU, nephelometric turbidity unit; Ph Eur, European Pharmacopeia; SE-HPLC, size exclusion high-performance liquid chromatography; USP, United States Pharmacopeia

Extractables and Leachables

Extractables and leachable in the glass syringe and chlorobutyl plunger stopper were addressed in a series of controlled extraction studies with different solvents under worst case scenario and storage conditions. The syringe is supplied by (b) (4)

and the chlorobutyl plunger stopper by (b) (4). They comply with the biological activity requirements specific in SUP <381>. (b) (4) provided the extractable data for syringe barrel, needle, and needle adhesive. The data for the plunger stopper

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was provided by (b) (4). Compounds identified in the extractable studies were extrapolated to represent Total Daily Intake (TDI, µg/day) and selected for potential leachability analysis. Elements at concentrations identified in the extractable studies were not considered a safety concern. Compounds and elements identified in the extraction studies with the stopper are listed in [Table 61](#).

Table 61. Chlorobutyl Rubber Extractable Study Compounds and Elements

Compound / Element	Extraction Solvent	Analysis Technique	Compound or Element Concentration µg/stopper	Plunger Stopper TDI µg/day
(b) (4)	(b) (4)	HS/GC/MS	(b) (4)	(b) (4)
		HS/GC/MS		
		HS/GC/MS		
		HS/GC/MS		
		HS/GC/MS		
		HS/GC/MS		
		HS/GC/MS		
		ICP/OES		
		ICP/OES		
		ICP/OES		
		ICP/MS		
		ICP/OES		
		ICP/OES		
		ICP/OES		
		ICP/OES		

Source: Applicant-provided table

Compounds/elements that are bolded were quantitated with standard (AUF not included in the TDI calculation).

Abbreviations: AUF, analytical uncertainty factor; HS/GC/MS, headspace/gas chromatography/mass spectrometry; ICP/MS, inductively coupled plasma/mass spectrometry; ICP/OES, inductively coupled plasma/optical emission spectroscopy, TDI, total daily intake

Leachability Study

The leachability study designed to identify the daily exposure to leachable compounds from the container (glass syringe and chlorobutyl plunger stopper) was based on notable compounds detected in the extractability study. The safety concern threshold (SCT) defined as 1.5 µg/day TDI for each mutagenic and 5 µg/day for non-mutagenic compounds per International Council for Harmonisation M7(R1) was applied to safety assessment of leachable compounds. Any compound exceeding 1.5 µg/day was identified and quantitated. Leachability studies have been completed for up to 12 months and long-term studies up to 60 months are ongoing. All organic compounds in the 6-month leachability tests were below the quantification limit with the exception of (b) (4) at (b) (4) µg/day ([Table 62](#)). Since all TDIs were lower than PDE (International Council for Harmonisation Q3C) and have established toxicological data by all routes, the Applicant did not carry any further risk assessment. However, the chemistry, manufacturing, and controls reviewer considered (b) (4) as potential concern and requested further safety assessment.

Table 62. Leachable Results for Drug Product Lot EH7901 PFS Stored at 2 to 8 °C: Leachable Studies and Data for 24, 36, 48 and 60 Months Yet To Be Determined

(b) (4)



Conclusion

In summary, compounds identified in the leachability studies coming from glass syringe and chlorobutyl plunger stopper were within the acceptable daily limits and do not pose a safety risk to humans. It should be noted that both the glass barrel pen and chlorobutyl plunger stopper are obtained from commercial sources and have been used with similar products.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Study #200064198 /Title: A 3-Month Intravenous or Subcutaneous Injection Toxicity and Toxicokinetic Study of PF-06741086 in Rats With a 6-Week Recovery Phase

Key Study Findings

- Minimal and nondose dependent decrease in prothrombin time, prolongation of APTT (at all doses), and lower FIB concentrations were observed during the study but not at the end of the recovery.
- There were no marstacimab associated adverse histopathology findings in rats.
- Non-neutralizing ADAs were detected in 9/32 (28.1%) treated animals (no change in drug exposure).
- No marstacimab related adverse findings were seen in rats. The top doses of 1000 mg/kg once weekly IV and 180 mg/kg once weekly SC were considered NOAELs in rats. Exposure at the NOAEL dose was 212X the exposure at the MRHD on AUC basis.

Table 63. Study Information, Study #200064198

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 180, (180 SC) or 1000 mg/kg/dose, once weekly
Route of administration	IV up to 1000 mg/kg, SC 0, or 180 mg/kg
Formulation/vehicle	vehicle (20 mM histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, 0.2 mg/mL polysorbate-80, pH 5.8)
Species/strain	Crl:WI(Han) rats
Number/sex/group	10/sex/group +5/sex/control and HD recovery
Age	10 weeks
Satellite groups/unique design	3-4/sex/group
Deviation from study protocol affecting interpretation of results:	No meaningful impact on the findings

Source: Applicant-provided data

Abbreviations: EDTA, ethylenediaminetetraacetic acid; GLP, good laboratory practice; HD, high dose; SC, subcutaneous

Table 64. Observations and Results, Study #200064198

Parameters	Major Findings
Mortality	No marstacimab-related deaths
Clinical signs	Unremarkable
Body weights	No marstacimab -related effect
Ophthalmoscopy	No marstacimab -related effect
Electrocardiogram	Not done
Hematology	Minimal decrease in PT (0.93X control), increased in aPTT (1.1 to 1.2X control), and lower FIB (0.79 to 0.81X the control) concentrations in marstacimab-treated rats relative to control
Clinical chemistry	Slight increase in globulin (G), lower A:G ratio in both sexes at 1000 mg/kg.

Parameters	Major Findings
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Table 65. Hematological Changes in Rats Treated With Marstacimab for Three Months

Parameter	Group Dose Day	Dose Level (mg/kg/dose)											
		Male						Female					
		1	2	3	4	5	6	1	2	3	4	5	6
		Control IV [®]	Control SC [®]	60 mg/kg IV	180 mg/kg IV	180 mg/kg SC	1000 mg/kg IV	Control IV [®]	Control SC [®]	60 mg/kg IV	180 mg/kg IV	180 mg/kg SC	1000 mg/kg IV
PT (sec)	15	11.4	11.1	-	-	-	-	10.4	10.5	-	-	-	-
	29IV/32SC	11.7	10.9	-	-	0.93x	-	10.8	9.8	-	-	0.93x	-
	50	11.1	10.9	-	-	-	-	10.4	10.1	-	-	-	0.90x
	93/94	11.9	12.2	-	-	-	-	10.3	10.5	-	-	-	-
APTT (sec)	15	17.5	18.0	-	-	-	-	17.9	18.4	-	-	-	-
	29IV/32SC	16.8	16.4	1.12x^a	1.17x	1.20x	1.13x	18.5	18.5	-	-	1.07x	-
	50	15.9	16.2	1.10x	1.09x	1.10x	1.11x	16.4	17.7	1.09x	1.12x	1.07x	1.13x
	93/94	16.1	15.9	-	-	-	-	14.1	16.1	1.18x	1.14x	-	1.23x
FIB (mg/dL)	15	266	262	-	-	-	-	217	212	0.90x	0.89x	0.90x	0.89x
	29IV/32SC	270	271	-	-	-	0.79x	198	207	-	-	-	0.81x
	50	284	285	-	-	-	-	217	202	0.86x	0.86x	-	0.80x
	93/94	232	238	-	-	-	-	174	160	0.86x	0.89x	-	-

Source: Applicant's data table

^a The fold change (x) reported for test article-dosed groups was determined by dividing the test article-dosed group mean value at each time point by the control group mean value.^b IV groups (Groups 1, 3, 4, and 6) were sampled on Day 29; SC groups (Groups 2 and 5) were sampled on Day 32.[®] numerical values for control groups represent the absolute mean values.

() indicates no test article-related change. Bolded values indicate statistical significance (p≤0.05).

Abbreviations: aPTT, activated partial thromboplastin time; FIB, fibrinogen concentration;

IV, intravenous; PT, prothrombin time; SC, subcutaneous

Urinalysis No drug-related effect

Gross pathology No drug-related effect

Organ weights No drug-related effect

Histopathology Yes

Adequate battery:

Source: Study #200064198

Abbreviations: A, albumin; aPTT, activated partial thromboplastin time; FIB, fibrinogen concentration; G, globulin; PT, prothrombin time

Study #0062114/Title: A 3-Month Intravenous or Subcutaneous Injection Toxicity and Toxicokinetic Study of PF-06741086 in Cynomolgus Monkeys With a 6-Week Recovery Phase**Key Study Findings**

- Contradictory to marstacimab PD, there was no change in prothrombin time and aPTT and decrease in FIB concentrations (~60%). Marstacimab treated monkeys however had significant increase in DDIM (marker of blood clot) supported some marstacimab-related pharmacological activity in monkeys.
- The single minimal acute incidence of lung emboli at low dose of 30 mg/kg/week IV was not considered marstacimab-related based on the lack of similar findings in other animals at any dose levels and lack of similar findings in other tissues.
- There were no detectable ADAs in marstacimab treated monkeys given by IV or SC route.
- There were no adverse histopathology findings in monkeys. The top doses of 500 mg/kg/wk IV and 90 mg/kg/wk SC were considered NOAELs. Exposure at the IV NOAEL was about

HYMPAVZI (marstacimab-hncq) injection

219X the exposure at the MRHD dose on AUC basis (300 mg SC once weekly, AUC_{168h}, 9146 µg.h/mL). Exposure at the SC dose of 90 mg/kg was roughly 40X the exposure at the MRHD on AUC basis.

Table 66. Study Information, Study #0062114

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 30, 90, (90 SC) or 500 mg/kg/dose, once weekly
Route of administration	IV up to 500 mg/kg, SC (0 or 90 mg/kg)
Formulation/vehicle	Vehicle (20 mM histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, 0.2 mg/mL polysorbate-80, pH 5.8)
Species/strain	Mauritius Cynomolgus monkeys
Number/sex/group	3/sex/group +2/sex/ control and HD recovery
Age	3.7 to 7.2 years
Satellite groups/unique design	None
Deviation from study protocol affecting interpretation of results:	None

Source: Generated from Applicant's study

Abbreviations: EDTA, ethylenediaminetetraacetic acid; GLP, good laboratory practice; HD, high dose; IV, intravenous; SC, subcutaneous

Table 67. Observations and Results, Study #0062114

Parameters	Major Findings
Mortality	No deaths
Clinical signs	Unremarkable
Body weights	No marstacimab-related effect
Ophthalmoscopy	No marstacimab-related effect
Electrocardiogram	No marstacimab-related effect
Hematology	Non-adverse marstacimab-related minimal to mild increase in PT (1.1X to 1.3X baseline), aPTT (1.1X to 1.16 X baseline) and decrease in FIB (0.56X to 0.8X the baseline) and D-dimer (1.2X to 4.42X baseline). Except for D-dimer, they were comparable to control values at the end of the recovery phase. There was no clear dose-response relationship.

Table 68. Hematological Changes in Monkeys Treated With Once Weekly Marstacimab for 3 Months

Dose* (mg/kg/week)	0 (Control) (IV and SC)		30 (IV)		90 (IV)		500 (IV)		90 (SC)	
Sex	M	F	M	F	M	F	M	F	M	F
Hematology/Coagulation										
Prothrombin Time (sec)										
Baseline	12.26	12.28	12.50	11.80	12.13	11.83	12.20	11.46	12.07	11.87
Day 29	11.86	12.74	13.27*	12.77	12.93*	12.67	13.88*	13.02	12.60	12.70
Day 92	13.20	13.74	13.73	13.37	14.40	12.87	14.36	13.52	13.97	15.47
APTT (sec)										
Baseline	21.90	-	22.27	-	22.33	-	21.76	-	23.07	-
Day 29	22.06	-	22.03	-	23.13	-	25.14	-	23.20	-
Day 92	21.32	-	22.43	-	22.13	-	23.96	-	23.07	-
Fibrinogen (mg/dL)										
Baseline	246.00	246.80	255.67	231.00	258.67	240.00	243.00	232.40	310.33	215.67
Day 29	209.00	211.40	149.33	150.67*	175.33	148.67*	135.20*	140.60*	187.00	173.00
Day 92	206.80	242.20	171.67	160.00*	164.67	193.33	161.80	161.80*	251.33	169.00
D-Dimer (µg/mL)										
Baseline	1.03	0.66	1.35	1.05	1.38	0.60	1.27	1.12	1.84	1.10
Day 29	0.49	0.81	2.29*	2.40	2.45*	2.65*	2.51*	2.68*	2.33*	2.55*
Day 92	0.78	0.52	2.25*	1.93*	2.40*	2.20*	2.31*	2.27*	2.20*	2.34*

Source: Applicant-provided table

Abbreviations: APTT, activated partial thromboplastin time; F, female; IV, intravenous; M, male; SC, subcutaneous

Parameters	Major Findings
Clinical chemistry	Slight increase in globulin (1.08X to 1.57X baseline), lower A:G ratios in both sexes at HD relative at some timepoints relative to corresponding controls was observed. The clinical significance of the increase in globulin was not clear.

Table 69. Changes in Clinical Chemistry Parameters in Monkeys

Dose* (mg/kg/week)	0 (Control) (IV and SC)		30 (IV)		90 (IV)		500 (IV)		90 (SC)	
Sex	M	F	M	F	M	F	M	F	M	F
Clinical Chemistry										
Globulin (g/dL)										
Baseline	3.38	3.70	3.50	3.70	3.40	3.83	3.50	3.64	3.53	3.67
Day 29	3.26	3.60	3.57	4.07	3.93*	4.43*	5.36*	5.70*	3.83*	4.40*
Day 92	3.04	3.40	3.27	3.67	3.53	3.70	4.26*	4.48*	3.97*	3.73
Total Protein (g/dL)										
Baseline	7.72	7.76	7.63	7.77	7.47	7.97	7.68	7.78	7.63	7.73
Day 29	7.92	7.62	8.07	8.20	8.13	8.53*	9.38*	9.42*	8.10	8.47*
Day 92	7.50	7.54	7.60	7.57	7.77	7.80	8.50*	8.46*	8.20*	7.70
Albumin/Globulin Ratio										
Baseline	1.30	1.08	1.20	1.10	1.20	1.10	1.20	1.16	1.17	1.10
Day 29	1.44	1.12	1.27	1.03	1.03*	0.93	0.76*	0.64*	1.13*	0.93
Day 92	1.48	1.26	1.37	1.07	1.20	1.10	1.00*	0.90*	1.10	1.10

Source: Applicant-provided table

Abbreviations: F, female; IV, intravenous; M, male; SC, subcutaneous

Urinalysis	No drug-related effect
Gross pathology	No drug-related effect. Discoloration was noted at the site IV injection in 2 animals.
Organ weights	No drug-related effect
Histopathology	Histopath Evaluation:
Adequate battery:	A single incidence of minimal, acute thrombi/emboli in a small arteriole in the lung of one animal (Animal No. 2001) at low dose of 30 mg/kg/dose IV was not considered marstacimab-related based on the absence of similar findings in other animals treated with more than 30-fold higher doses of marstacimab. It should be noted that small thrombi/emboli do occasionally occur in the lung in monkeys following intravenous injections (Sato et al. 2012).
Yes	Histopathological evaluation of recovery animals appeared to be incidental and similar among groups including control.

Table 70. Lung Histopath Findings in Monkeys

Removal Reason: TERMINAL EUTHANASIA	Male				Female			
	0 mg/kg/ dose	30 mg/kg/ dose	90 mg/kg/ dose	500 mg/kg/ dose	0 mg/kg/ dose	30 mg/kg/ dose	90 mg/kg/ dose	500 mg/kg/ dose
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Number of Animals:	3	3	3	3	3	3	3	3
LUNG								
Examined	3	3	3	3	3	3	3	3
No Visible Lesions	2	2	3	2	3	3	3	3
Hemorrhage; alveolar	1	0	0	0	0	0	0	0
.... minimal	1	0	0	0	0	0	0	0
Inflammation, mononuclear cell; interstitial	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
Inflammation, mixed cell; alveolar, interstitial	0	0	0	0	0	0	0	0
.... mild	0	0	0	0	0	0	0	0
Infiltration, mononuclear cell; interstitial	0	1	0	0	0	0	0	0
.... mild	0	1	0	0	0	0	0	0
Thrombi/emboli; acute	0	1	0	0	0	0	0	0
.... minimal	0	1	0	0	0	0	0	0

Source: Applicant Provided Data

Source: Study #0062114

Abbreviations: A, albumin; aPTT, activated partial thromboplastin time; FIB, fibrinogen concentration; G, globulin; IV, intravenous; PT, prothrombin time

Study #20089324 /Title: A 6-Month Intravenous Bolus Injection Toxicity Study of PF-06741086 in Rats With a 6-Week Recovery Period**Key Study Findings**

- Marstacimab increased prothrombin time at 1000 mg/kg/wk in both sexes and contrary to pro-coagulatory effect, marstacimab increased APTT and DDIM and decreased FIB at all doses in both sexes
- Minimal Acute marstacimab-related evidence of thrombi/emboli with no secondary tissue injury was observed the lungs and tail vein injection sites at ≥ 60 mg/kg/wk.
- In contrast to the 3-month rat study, there were no detectable ADA in the 6-month rat study. Based on minimal nonadverse findings, the top weekly IV dose of 1000 mg/kg ($AUC_{168h} = 1,840,000 \mu g \cdot h/mL$) was considered the NOAELs in rats and the exposure was 201X the exposure at the MRHD on AUC basis ($AUC_{168h} 9146 \mu g \cdot h/mL$).

Table 71. Study Information, Study #20089324

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 60, 180 or 1000 mg/kg/ dose, once weekly
Route of administration	Intravenous (IV route, to increase exposure at maximum feasible dose)
Formulation/vehicle	Vehicle (20 mM histidine, 85 mg/mL sucrose, 0.05 mg/mL disodium EDTA, 0.2 mg/mL polysorbate-80, pH 5.8)
Species/strain	Crl:WI (Han) rats
Number/sex/group	10/sex/group +5/sex/group
Age	9 weeks
Satellite groups/unique design	3-4/sex/group
Deviation from study protocol	None
affecting interpretation of results:	

Source: Derived from Applicant's study report

Abbreviations: EDTA, ethylenediaminetetraacetic acid; IV, intravenous

Table 72. Observations and Results, Study 20089324

Parameter	Major Findings
Mortality	No deaths
Clinical signs	Unremarkable
Body weights	No marstacimab-related effect
Ophthalmoscopy	No marstacimab-related effect
Electrocardiogram	Not done
Hematology	No significant hematological changes. Minimal increase in PT at high dose of 1000 µg/kg/wk (1.04X to 1.12X control), Minimal increase in aPTT (1.06X to 1.19X control) and DDIM (1.37X to 5.33X control) and decrease in FIB (0.76X to 0.94X control) at ≥60 µg/kg/wk. Although expected a decrease in clotting parameters, there were small increases in PT, aPTT and decrease in fibrinogen.

Table 73. Effect on Coagulatory Parameters in Rats Relative to Control (60, 180 or 1000 mg/kg/wk) PF-06741086

PF-06741086 Dose (mg/kg/dose)									
Parameter	Males					Females			
	Day	0	60	180	1000	0	60	180	1000
PT (sec)	50	11.44	—	—	1.12x	10.64	—	—	1.06x
	92	11.78	—	—	1.11x	10.87	—	—	1.06x
	127	11.54	—	—	1.09x	10.75	—	—	1.04x
	182/183	11.73	—	—	1.09x	10.51	—	—	1.06x
APTT (sec)	50	17.09	1.09x	1.13x	1.05x	17.15	1.19x	1.11x	1.10x
	92	17.45	1.07x	—	—	—	—	—	—
	127	17.58	1.06x	1.08x	—	18.65	—	1.06x	1.06x
	182/183	15.73	1.06x	1.08x	1.08x	17.63	—	—	1.07x
FIB (mg/dL)	50	298.07	0.94x	0.90x	0.78x	204.47	—	0.88x	0.77x
	92	299.92	—	—	0.84x	171.85	—	—	0.94x
	127	299.67	—	—	0.76x	182.27	—	0.91x	0.77x
	182/183	300.08	—	0.93x	0.77x	169.90	0.94x	0.92x	0.81x
DDIM (ug/mL)	92	0.26	—	1.37x (5/15)	1.43x (5/14)	0.14	2.17x (2/14)	—	3.68x (2/10)
	127	0.18	—	3.91x (2/13)	3.86x (8/15)	0.22	2.35x (3/11)	-	3.19x (6/15)
	182/183	0.17	3.28x (4/11)	—	5.33x (7/15)	0.27	2.12x (3/12)	—	2.26x (3/13)

Source: Applicant provided study

Bolded values indicate statistical significance (p≤0.05). Fractions in parenthesis reflect the incidence of changes in D-dimer within the groups.

Abbreviations: APTT, activated partial thromboplastin time; FIB, fibrinogen concentration, DDIM, D-dimer concentration; PT, prothrombin time

Parameter	Major Findings
Clinical chemistry	Slight increase in globulin, total protein, and lower albumin:globulin ratio in both sexes at ≥ 180 $\mu\text{g/kg/wk}$.

Table 74. Effect on Notable Clinical Chemistry Parameters Relative to Control Rats PF-06741086

Parameter	PF-06741086 Dose (mg/kg/dose)							
	Males				Females			
Dose	0	60	180	1000	0	60	180	1000
TPROT (g/dL)	6.03	–	1.05x	1.27x	6.30	–	1.06x	1.20x
ALB (g/dL)	3.14	–	–	0.89x	3.59	–	–	0.96x
GLOB (g/dL)	2.89	–	1.13x	1.68x	2.73	1.06x	1.12x	1.51x
A/G ratio	1.09	–	0.89x	0.54x	1.31	–	0.90x	0.64x

Source: Applicant provided study

Bolded values indicate statistical significance ($p \leq 0.05$).

Abbreviations: A/G, albumin/globulin ratio; ALB, albumin; GLOB, globulins; TPROT, total proteins

Urinalysis	No marstacimab-related effect
Gross pathology	No marstacimab-related effect. However, dark focused discolorations were noted in the thymus among all groups including control. They correlated with acute hemorrhage observed microscopically. Since they were observed also in control, the relation to marstacimab is not clear and likely were associated to old age.
Organ weights	No marstacimab-related effect
Histopathology	Histopathology findings were observed in the lung and tail vein injection site.
Adequate battery: Yes	The lung findings included acute minimal emboli in males (C:0, LD:2, MD3, HD:1) and females (C:0, LD:1, MD:0, HD:4), minimal cellular infiltrate with refractile material in the lung, and minimal basophilic or nonbasophilic (light gray or clear) foreign material in the lung at ≥ 60 mg/kg/dose in males and/or females. There were no such findings in the 3m rat or monkeys treated with marstacimab doses up to 1000 mg/kg/wk. In the tail vein, the minimal thrombi/emboli (acute and organizing) were observed at the injection site at ≥ 180 mg/kg/dose in males and at ≥ 60 mg/kg/dose in females. Acute minimal thrombi/emboli at the injection site were characterized by pale staining eosinophilic granular to fibrillar material within the very small vessel. Although thrombi/emboli are common at venipuncture sites; the minimal increase in incidence in the emboli in lungs compared with controls appear to correspond with the expected drug pharmacology, however, in absence of secondary effect at the site of emboli and increase in PT and aPTT, the relation to marstacimab is not clear. Based on minimal incidence and acute nature of emboli in some treated animals, it is highly possible that emboli were triggered during the last stage of the study, i.e., euthanasia/exsanguination.

Parameter	Major Findings
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Table 75. Microscopic Findings in Wistar Hans Rat Treated With Marstacimab for Six Months

	Male Dose (mg/kg/dose)				Female Dose (mg/kg/dose)			
	0	60	180	1000	0	60	180	1000
Lung ^a	15	15	15	15	15	15	15	15
Thrombi/emboli; acute								
Minimal	-	2	3	1	-	1	-	4
Thrombi/emboli; organizing								
Minimal	-	1	4	1	-	1	2	-
Infiltrate with refractile material								
Minimal	-	5	6	10	2	4	5	12
Foreign material, (basophilic or non-basophilic)								
Minimal	1	-	2	5	-	1	3	2
Injection site, tail vein	15	15	15	15	15	15	15	15
Thrombi/emboli; acute								
Minimal	-	-	2	2	-	1	-	1
Thrombi/emboli; organizing								
Minimal	-	-	-	1	-	-	1	-

- No finding present.

^a Number of animals examined.

Source: Applicant-provided data

Source: Applicant-provided data

Abbreviations: aPTT, activated partial thromboplastin time; C, control; DDIM, D-dimer concentration; FIB, fibrinogen concentration, HD, high dose; LD, low dose; MD, middle dose; PT, prothrombin time

13.2.1. Reproductive Toxicology

Study #00655204 / Title: A Fertility and Early Embryonic Development Study of PF-06741086 by Intravenous Injection in Male Wistar Rats

Key Study Findings

- Marstacimab treated males up to 1000 mg/kg/wk, mated with native females did not affect male reproductive performance or spermatogenesis neither pregnancy, implantation, nor embryonic survival in untreated pregnant females.
- Plasma concentration at 5 min post 1000 mg/kg in male rats (5,0800,000 ng/mL) was consistent with drug exposure in toxicity studies, thus AUC for exposure multiple was based on 6-month rat study. Based on existing AUC data, the exposure in males was estimated to be 212X the exposure at the MRHD of 300 mg on AUC basis.
- The top dose of 1000 mg/kg/wk was accepted as NOAEL. Exposure at the NOAEL dose was 201X the exposure at the MRHD of 300 mg per week on AUC basis.

Good Laboratory Practice compliance: Yes

Table 76. Methods of Fertility and Early Embryonic Developmental Study in Male Rats, Study #00655204

Parameter	Method Details
Dose and frequency of dosing	60, 180 or 1000 mg/kg/week
Route of administration	Intravenous
Formulation/vehicle	20 mM histidine, 85 mg/mL sucrose, 0.2 mg/mL polysorbate 80, and 0.05 mg/mL disodium-EDTA, pH 5.8
Species/strain	Wistar Hans male rats (CrI: WI(Han) plus naïve Wistar Hans female rats
Number/sex/group	20/sex/group (females were not dosed)
Satellite groups	no
Study design	Males Wistar rats dosed intravenously once weekly with marstacimab up to 1000 mg/kg (total 11 doses, at least 4 wks prior to mating). Plasma samples were collected at 5 min post dose. Males were termination on Day 71/72 while females were termination on Gestation Day 14 (GD14) for necropsy. Animals were euthanized by carbon dioxide inhalation. The study did not include a TK group. Blood samples collected at the end of the study from males was used to determine marstacimab exposure.
Deviation from study protocol affecting the interpretation of results	Minor with no impact on the study. Plasma samples collected for ADA analysis were not evaluated. Previous studies have shown no notable ADA in rats treated with marstacimab for up to 6 months.

Source: Applicant-provided report

Abbreviations: ADA, antidrug antibody; EDTA, ethylenediaminetetraacetic acid; GD, gestation day; TK, toxicokinetic

Table 77. Observations and Results, Study #00655204

Parameter	Major Findings
Mortality	No deaths or effect on survival
Clinical signs	No marstacimab-associated clinical signs
Body weights	No adverse or significant changes
Reproductive performance	Marstacimab had no effect in male rats' reproductive performance, i.e., mating, fertility and copulation indices or pre-coital intervals. Embryonic data collected from untreated females mated with marstacimab-treated males found no marstacimab-related changes in number of viable embryos, total resorptions, pre- or post-implantation loss, corpora lutea or number of gravid females at necropsy at the study termination.
Spermatogenic evaluation	Marstacimab had no effect on spermatogenesis endpoints, i.e., mean cauda epididymal sperm numbers or sperm motility, epididymal weight
Necropsy findings	There were no gross or microscopic findings in male rats.
Offspring	Marstacimab treated males mated with native females did not affect the pregnancy, implantation, or embryonic survival in untreated pregnant females. The top weekly IV dose of 1000 mg/kg was considered NOAEL.
PK analysis	Plasma concentrations of marstacimab were determined at 5 min post dose on Day 70 (plasma 50,800,000 ng/mL). No additional samples were collected or analyzed for ADA. Based on existing 3-month rat PK data at 1000 mg/kg., the exposure multiples provided by 1000 mg/kg marstacimab was greater than 200-times the exposure at the MRHD of 300 mg on AUC basis.

Source: Applicant study data

Abbreviations: ADA, antidrug antibody(ies); AUC, area under the concentration-time curve; IV, intravenous; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; PK, pharmacokinetic

14. Clinical Pharmacology

14.1. In Vitro Studies

In patients with hemophilia who develop inhibitors⁴, the Applicant proposes that bypass agents⁵, such as recombinant Factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC) may be used to treat breakthrough bleeds while on marstacimab prophylaxis. Therefore, the Applicant conducted in vitro drug-drug interaction studies to evaluate the potential additive effect of marstacimab and the bypass agents on coagulation parameters.

Marstacimab When Used in Combination With rFVIIa, Study #122443

The additive effect of marstacimab and rFVIIa on thrombin generation in hemophilic plasma with or without inhibitors was evaluated using the TGA. The peak thrombin levels when rFVIIa and marstacimab were administered alone or in combination in plasma of patients with HA with or without inhibitor, and HB without inhibitor are provided in [Table 78](#). Marstacimab concentration of 16 µg/mL was selected to approximate steady state maximum plasma concentration (C_{max}) based on modeling of 2 mg/kg subcutaneous dose. The $C_{max,ss}$ based on the population PK modeling of 150 mg SC weekly dose (with loading dose of 300 mg) is 19.7 µg/mL. The peak thrombin level when marstacimab was administered alone (82 to 172nM, 88 to 166nM, and 174nM) or in combination with rFVIIa (102 to 178nM, 99 to 57nM, and 167nM) was comparable in plasma of patients HA with or without inhibitors and HB without inhibitor, respectively, demonstrating minimal additive effect.

Table 78. Peak Thrombin Levels for Marstacimab and rFVIIa When Used Alone or in Combination

Group	Vehicle	rFVIIa 2 µg/mL	PF-06741086 (16 µg/mL)	PF-06741086 (16 µg/mL) rFVIIa (2 µg/mL)	Non- Hemophilic	Non- Hemophilic PF-06741086 (16 µg/mL)
Hemophilia A (n = 6)	26 – 76 nM	45 – 113 nM	82 – 172 nM	102 - 178 nM	128 – 135 nM	198 nM (n = 1)
Hemophilia A with Inhibitor (n = 3)	24 – 66 nM	46 – 89 nM	88 - 166 nM	99 - 157 nM	130 – 132 nM	198 – 199 nM
Hemophilia B (n = 1)	81 nM	131 nM	174 nM	167 nM	143 nM	171 nM

Source: Table 10.1, page 14 of Study 122443 report

Vehicle=50% phosphate buffered saline/50% HEPES buffer; PF-06741086=marstacimab.

Abbreviations: n, number of participants in specific group; rFVIIa, recombinant factor VIIa

⁴ Inhibitor: neutralizing antibody to the injected factors, FVIII or FIX

⁵ Bypass agent: a treatment that helps blood clot by activating the coagulation cascade without the need for FVIII or FIX

Marstacimab When Used in Combination With aPCC, Study #045123

The effect of marstacimab in promoting coagulation when used in combination with plasma derived aPCC was evaluated using the TGA in platelet poor plasma from patients with HA with inhibitor and patients with HB with inhibitor. The peak thrombin level using the TGA is shown in [Table 79](#). The peak thrombin levels when marstacimab was used in combination with aPCC (209.3 to 240.6nM and 254.1nM in hemophilia A and B, respectively) were higher than marstacimab (72.9 to 109.7nM and 70.1nM in hemophilia A and B, respectively) or aPCC (74.7 to 110.1nM and 163.1nM in hemophilia A and B, respectively) alone. However, the thrombin levels when used in combination were still within the range of marstacimab in nonhemophilic plasma (182.1 to 256.7nM and 160.4nM in hemophilia A and B, respectively) which would have full complement of coagulation factors.

Table 79. Peak Thrombin Levels for Marstacimab and aPCC When Used Alone or in Combination

Group	Vehicle	Non-hemophilic plasma*	aPCC (FEIBA®) 1 U/mL	Non-hemophilic plasma PF-06741086 16 µg/mL*	PF-06741086 16 µg/mL	PF-06741086 16 µg/mL aPCC (FEIBA®) 1 U/mL
HA 88 – 160 BU (n = 4)	14.6 - 19.05 nM	94.91 - 135.23 nM	74.73 - 110.08 nM	182.13 - 256.73 nM	72.92 - 109.69 nM	209.26 - 240.57 nM
HB 14 BU (n = 1)	30.51 nM	89.62 nM	163.08 nM	160.43 nM	70.14 nM	254.11 nM

Source: Table 10.1, page 13 of Study 045123 report

Vehicle=50% PBS/50% aPCC diluent; PF-06741086=marstacimab.

Abbreviations: aPCC, activated prothrombin complex concentrate, BU, Bethesda unit; FEIBA, factor eight inhibitor bypassing activity; HA, hemophilia A; HB, hemophilia B; PBS, phosphate buffered saline

14.2. In Vivo Studies

Study B7841001

A randomized, double-blind, sponsor-open, placebo-controlled, single IV or SC dose escalation study to evaluate the safety, tolerability, PK, and PD of PF-06741086 (marstacimab) in healthy participants and an open-label evaluation in healthy Japanese participants.

Primary Objective

To determine the safety and tolerability of marstacimab administered to healthy participants as single escalating SC administered doses or single escalating IV infused doses.

Study Design

This was a first-in-human, randomized, double-blind, sponsor-open, placebo-controlled study to investigate the safety, tolerability, PK, and PD of SC and IV administration of marstacimab. The study was conducted in seven planned cohorts of healthy male adult participants (Cohorts 1 through 7) and in an additional cohort of healthy Japanese male participants (Cohort 8). Participants were enrolled in a dose escalating fashion and randomized to either marstacimab or placebo (3:1 ratio) at doses of 30 mg (N=4), 100 mg (N=8), and 300 mg (N=8) subcutaneously

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and 150 mg (N=8), 300 mg (N=8), and 440 mg (N=8) intravenously. Japanese participants were enrolled into an additional single dose cohort (N=4) at marstacimab 300 mg SC. The pharmacokinetic sampling were done at predose, and 1, 4, 12, 24, 48, 72 hours, and 7, 14, 21, 28, 35, 42, 56, 70, and 84 days after SC dosing and at predose, and 1, 2, 4, 8, 12, 24, 48, 72 hours, and 7, 14, 21, 28, 35, 42, 56, 70, and 84 days after IV dosing. The pharmacodynamic samples such as TFPI level, TGA, prothrombin fragment 1+2, D-dimer, and diluted prothrombin time were collected at the same time as PK samples. The immunogenicity samples were collected at predose and 14, 21, 28, 35, 42, 56, 70, and 84 days postdose.

Results

Summary of PK parameters for marstacimab following single dose administration are provided in [Table 80](#). The median plasma marstacimab concentration versus time profiles for SC and IV administration are provided in [Figure 19](#). The PK parameters were not determined for the 30 mg SC cohort due to all concentrations below limit of quantification (BLQ). The Applicant noted that participants in the 150 mg IV cohort were slightly under-dosed due to an incorrect pump setting; however, the actual dose of 147 mg was accurately captured. The median time to reach C_{max} was 48 to 108 hours following SC administration. Regardless of route of administration (SC or IV), the exposure of marstacimab (C_{max} and AUC) increased with increasing dose in a greater than dose proportional manner. The clearance also decreased with increasing dose and the half-life increased from 33.3 hours to 65.8 hrs following 100 mg and 300 mg SC administration, respectively. The nonlinear PK is likely due to the target-mediated drug disposition. The exposure was comparable between Japanese and non-Japanese participants following 300 mg SC administration.

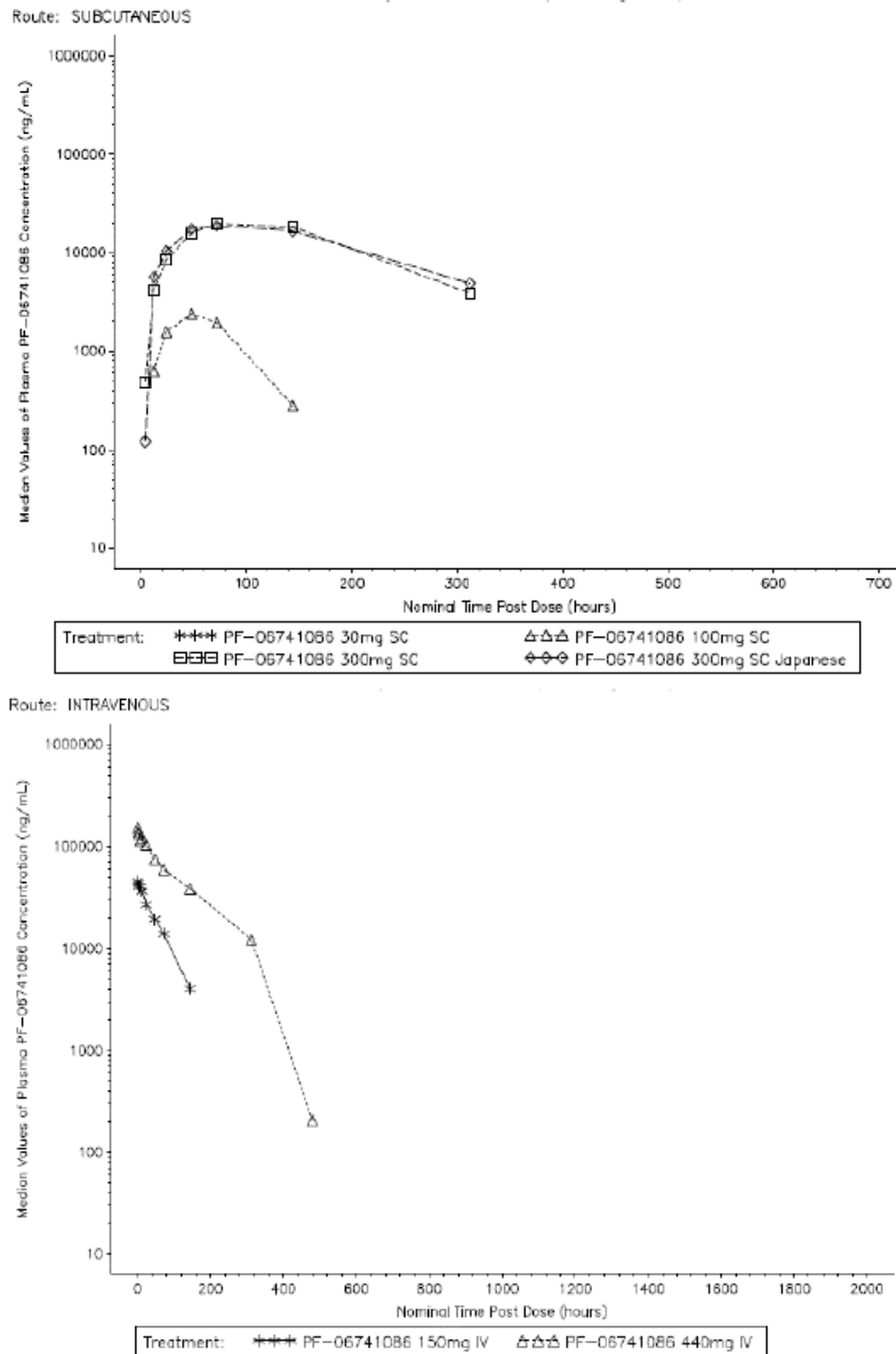
Table 80. Summary of Marstacimab Pharmacokinetic Parameters Following Single SC and IV Doses

Parameter (units)	Parameter Summary Statistics ^a by PF-06741086 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	6, 6	6, 5
AUC _{inf} (ng•hr/mL)	NC	257700 (34)	2799000 (83)	4955000 (4240000-5670000)	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 _½ (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	18430 (31)	9900 (107)	8465 (7620-9310)	NA	NA
V _{ss} (L)	NA	NA	NA	NA	3.525 (8)	3.880 (17)

Source: Table 11, page 83 of Study B7841001 CSR

^a Geometric mean (geometric %CV) for all except median (range) for T_{max}; arithmetic mean ± SD for t_½.^b Median and range presented since N=2.^c The actual dose administered for PF-06741086 150 mg IV was 147 mg due to incorrect pump set and validation.Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}, maximum observed concentration; CL, clearance; CL/F, apparent clearance; IV, intravenous, N, number of participants contributing to the summary statistics; n, number of participants for t_½, AUC_{inf}, V_z/F (or V_{ss}) and CL/F (or CL); NA, not applicable; NC, not calculated; SC, subcutaneous, T_{max}, time to reach maximum observed concentration, t_½, elimination half-life, V_{ss}, volume of distribution at steady state V_z/F, apparent volume of distribution

HYMPAVZI (marstacimab-hncq) injection

Figure 19. Median Plasma Marstacimab Concentration vs. Time Profile Following SC (Top) and IV (Bottom) Administration (Semi-Logarithmic Scale)

Source: Figure 2, page 82 of Study B7841001 CSR

Abbreviations: IV, intravenous; PF-06721086, marstacimab; SC, subcutaneous

PD parameters are provided in [Table 81](#) and [Table 82](#), respectively. The median plasma concentration versus nominal collection time (log transformed) for total TFPI and PD markers relevant to coagulation pathway activation such as prothrombin fragment 1+2, D-dimer, dPT,

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and TGA peak thrombin generation are provided in [Figure 20](#), [Figure 21](#), [Figure 22](#), [Figure 23](#), and [Figure 24](#), respectively. The results show that the changes in total TFPI as well as PD markers persisted more than 7 days following single dose of marstacimab 300 mg SC.

Substantial changes were observed at 300 mg SC dose or all IV doses, although minor changes were still seen with lower SC doses compared to placebo.

Table 81. Summary of Maximum Change From Baseline for Pharmacodynamic Parameters by Cohort and Dose

Parameter (unit)	Placebo	PF-06741086					
	(N = 9)	30 mg SC (N = 4)	100 mg SC (N = 6)	300 mg SC (N = 6)	150 mg IV ^a (N = 6)	440 mg IV (N = 6)	300 mg SC Japanese (N = 4)
Total TFPI (ng/mL)							
Mean	30.57	19.00	8.22	83.83	74.83	176.67	100.00
(SD)	(17.79)	(26.85)	(12.08)	(46.29)	(21.30)	(44.08)	(46.78)
Prothrombin fragment 1+2 (pmol/L)							
Mean	29.3	47.0	356.0	757.8	810.3	1124.3	561.0
(SD)	(23.56)	(17.61)	(213.23)	(97.99)	(350.79)	(594.84)	(133.37)
D-dimer (µg/mL)							
Mean	0.3556	0.1175	0.3092	2.3942	1.0258	2.3058	1.5025
(SD)	(0.4779)	(0.1367)	(0.2046)	(1.9145)	(0.3531)	(2.3350)	(1.0971)
Dilute PT (sec)							
Mean	-15.03	-26.78	-28.35	-30.70	-36.73	-32.17	-26.45
(SD)	(22.08)	(16.98)	(17.14)	(12.54)	(20.97)	(11.72)	(9.77)
Thrombin generation lag time (min)							
Mean	-0.44	-1.50	-2.15	-2.73	-2.43	-0.97	-0.88
(SD)	(0.400)	(0.887)	(0.909)	(1.221)	(0.914)	(0.250)	(0.222)
Peak thrombin generation (nmol)							
Mean	39.93	93.18	114.45	139.00	151.03	109.13	128.40
(SD)	(26.17)	(24.59)	(20.27)	(31.54)	(23.91)	(23.32)	(21.31)
Endogenous thrombin generation (nmol•min)							
Mean	163.8	253.8	486.7	720.5	717.7	278.2	331.0
(SD)	(86.57)	(194.79)	(135.94)	(108.77)	(165.34)	(113.86)	(188.20)

Source: Table 13, page 86 of Study B7841001 CSR

Abbreviations: CSR, clinical study report; IV, intravenous; N, number of participants; PT, prothrombin time; SC, subcutaneous; SD, standard deviation; TFPI, tissue factor pathway inhibitor

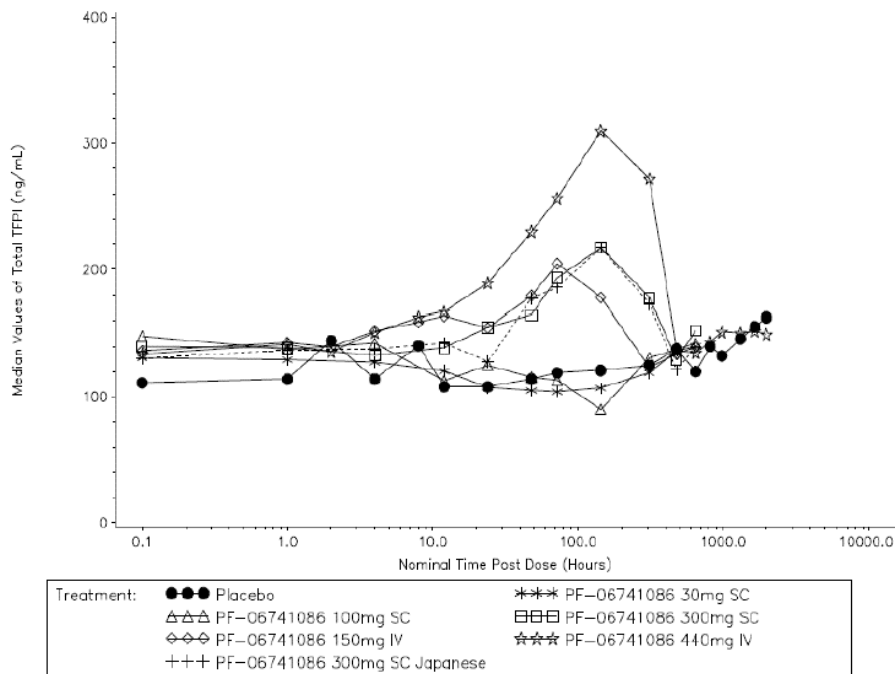
Table 82. Summary of AUC of Change From Baseline for Pharmacodynamic Parameters by Cohort and Dose

Parameter (unit)	Placebo	PF-06741086					
	(N = 9)	30 mg SC (N = 4)	100 mg SC (N = 6)	300 mg SC (N = 6)	150 mg IV ^a (N = 6)	440 mg IV (N = 6)	300 mg SC Japanese (N = 4)
Total TFPI (ng•hr/mL)							
Mean	1344	-1664	-4422	5757	6690	15558	8418
(SD)	(1398)	(1169)	(2253)	(2978)	(3188)	(3949)	(5525)
Prothrombin fragment 1+2 (pmol•hr/L)							
Mean	-1349	2244	31619	82084	78525	109093	61074
(SD)	(2624)	(1929)	(22874)	(11097)	(24816)	(69211)	(19355)
D-dimer (µg•hr/mL)							
Mean	7.74	7.51 (9.76)	22.37	133.68	110.28	139.07	145.91
(SD)	(13.95)		(19.52)	(84.63)	(41.83)	(120.91)	(105.50)
Dilute PT (sec•hr)							
Mean	1203	630 (1600)	-2200	-2368	-2618	-2346	-2277
(SD)	(2836)		(2408)	(2111)	(2447)	(1209)	(1522)
Thrombin generation lag time (min•hr)							
Mean	1.40	-89.30	-267.90	-342.07	-306.37	-92.97	-102.38
(SD)	(27.63)	(30.00)	(127.03)	(146.89)	(131.78)	(32.26)	(29.56)
Peak thrombin generation (nmol•hr)							
Mean	1293	5964	13629	15053	18031	10721	14627
(SD)	(1820)	(5275)	(3243)	(3554)	(2807)	(2125)	(2933)
Endogenous thrombin generation (nmol•min•hr)							
Mean	2910.6	24027.5	54408.5	75560.5	81910.5	12704.3	30766.5
(SD)	(10606.65)	(22917.96)	(17484.81)	(26836.37)	(29479.22)	(11315.89)	(23380.33)

Source: Table 14, page 87 of Study B7841001 CSR

Note: AUCs were calculated in participants with at least 75% of the total number of samples within the given interval available

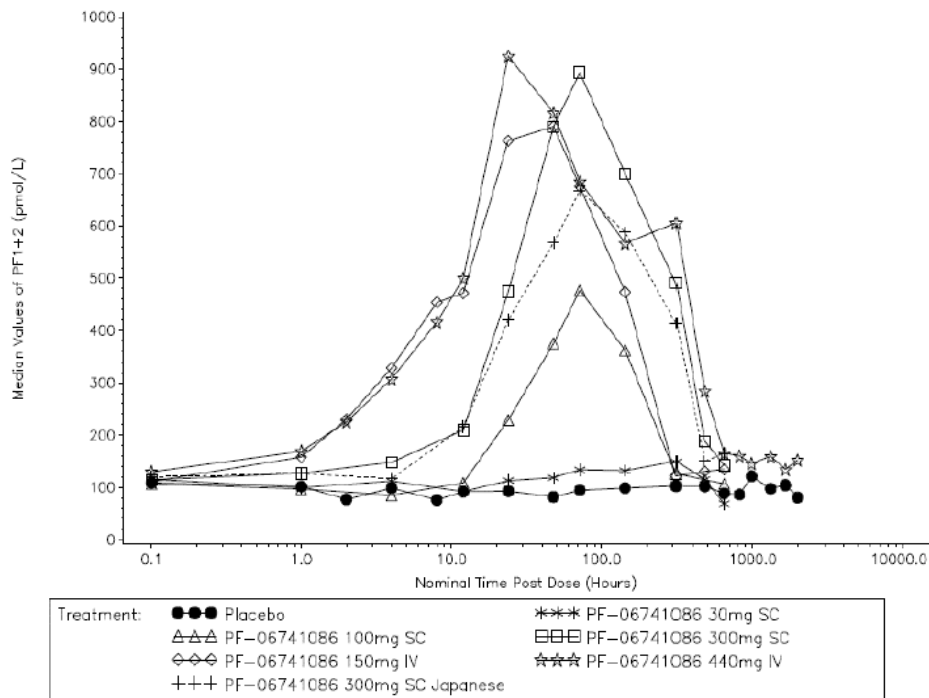
Abbreviations: AUC, area under the concentration-time curve; CSR, clinical study report; IV, intravenous; N, number of participants; PT, prothrombin time; SC, subcutaneous; SD, standard deviation; TFPI, tissue factor pathway inhibitor

Figure 20. Median Total TFPI vs. Time by Cohort and Dose

Source: Figure 4, page 88 of Study B7841001 CSR

Note: 0.1 hour in the figure represented Day 1 0 hour's readings

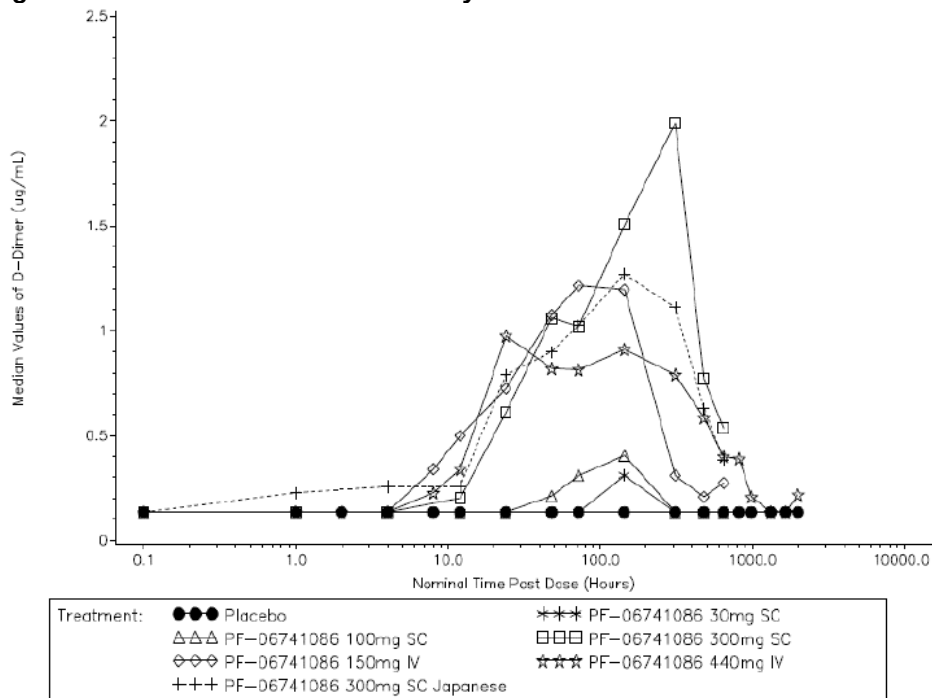
Abbreviations: CSR, clinical study report; IV, intravenous; SC, subcutaneous; TFPI, tissue factor pathway inhibitor

Figure 21. Median Prothrombin Fragment 1+2 vs. Time by Cohort and Dose

Source: Figure 5, page 89 of Study B7841001 CSR

Note: 0.1 hour in the figure represented Day 1 0 hour's readings

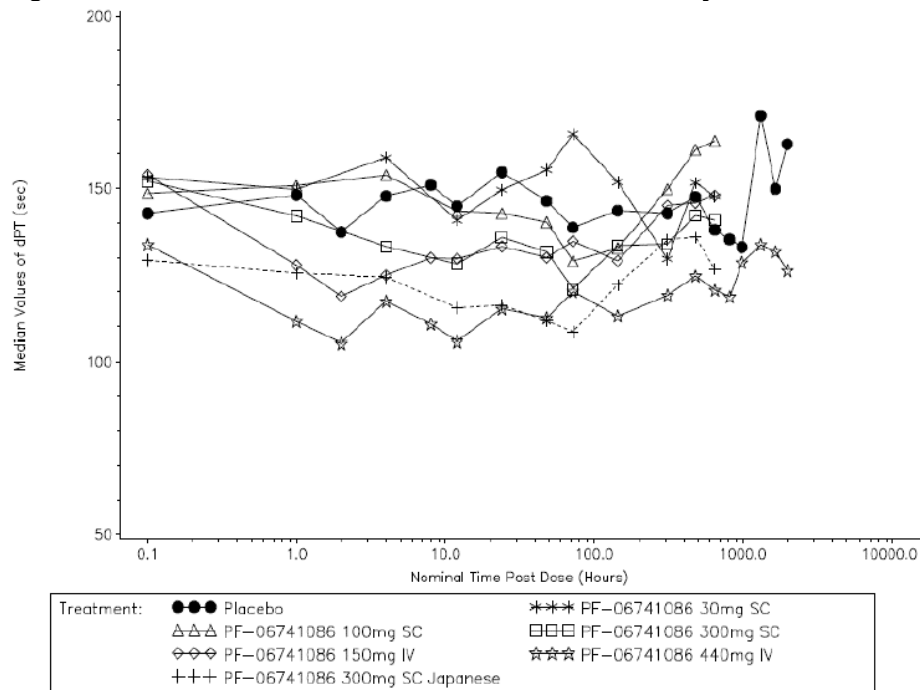
Abbreviations: CSR, clinical study report; IV, intravenous; PF, prothrombin fragment; SC, subcutaneous

Figure 22. Median D-Dimer vs. Time by Cohort and Dose

Source: Figure 6, page 90 of Study B7841001 CSR

Note: 0.1 hour in the figure represented Day 1 0 hour's readings

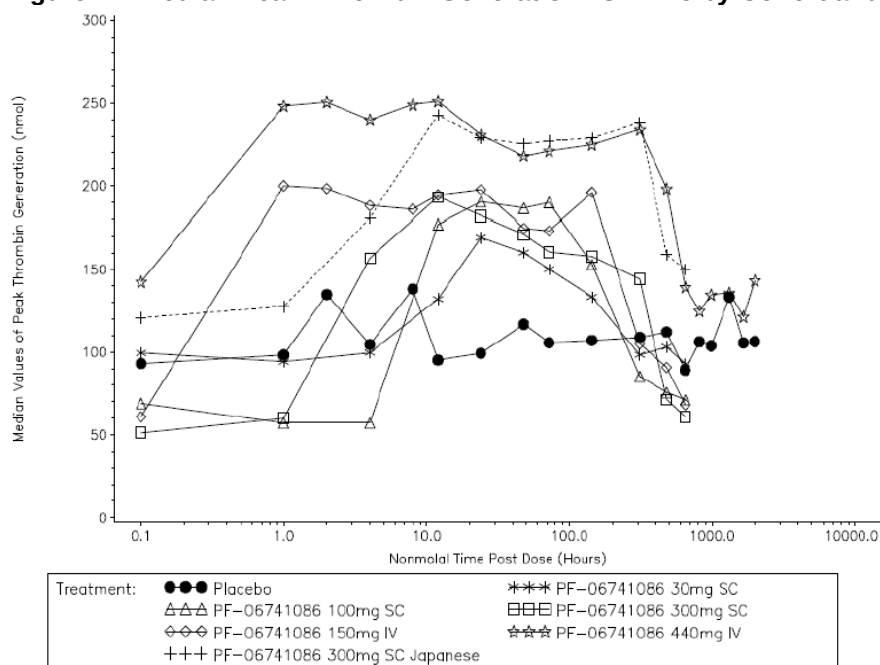
Abbreviations: CSR, clinical study report; IV, intravenous; SC, subcutaneous

Figure 23. Median Diluted Prothrombin Time vs. Time by Cohort and Dose

Source: Figure 6, page 90 of Study B7841001 CSR

Note: 0.1 hour in the figure represented Day 1 0 hour's readings

Abbreviations: CSR, clinical study report; dPT, diluted prothrombin time; IV, intravenous; SC, subcutaneous

Figure 24. Median Peak Thrombin Generation vs. Time by Cohort and Dose

Source: Figure 9, page 93 of Study B7841001 CSR

Note: 0.1 hour in the figure represented Day 1 0 hour's readings

Abbreviations: CSR, clinical study report; IV, intravenous; SC, subcutaneous

Study B7841002

A multicenter, open-label, multiple ascending dose study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of subcutaneous or intravenous PF-06741086 in participants with severe hemophilia.

Primary Objective

To determine the safety and tolerability of multiple doses of PF-06741086 administered to severe hemophilia A and B participants with and without inhibitors.

Study Design

This was a Phase 1b/2, open-label, multiple ascending dose study in male participants with severe hemophilia A or B, with or without inhibitors. The study consisted of four cohorts, starting at marstacimab 300 mg SC once weekly (Cohort 1, N=8, noninhibitors). Based on the safety, tolerability, and PK data through Day 29, lower dose of 150 mg SC once weekly with a loading dose of 300 mg (Cohort 2, N=6, noninhibitors) and higher dose of 450 mg SC once weekly (Cohort 3, N=6, noninhibitors) were initiated. Cohort 4 was originally intended for studying marstacimab 1000 mg IV once a month dosing regimen, however, Cohort 4 was modified to receive marstacimab 300 mg SC once weekly for participants with inhibitors only (N=7). The participants received treatment up to 3 months. The pharmacokinetic and pharmacodynamic sampling was done on Days 1, 2, 4, 8, 15, 22, 29, 30, 33, 57, 85, and 113. The immunogenicity sampling was done on Days 1, 15, 29, 57, 85 and 113.

Results

Summary of PK parameters following weekly marstacimab doses are provided in [Table 83](#). The median plasma marstacimab concentration versus time profiles for marstacimab are provided in [Figure 25](#). After multiple doses on Day 29 (Week 5), exposure (AUC_{τ} and $C_{\max}$) increased greater than dose-proportional over the range of 150 mg to 450 mg. Based on the trough concentrations, steady state appeared to have been achieved by Day 57. There was no significant difference in the exposure between participants with or without inhibitors based on marstacimab 300 mg weekly dose.

Table 83. Summary of Plasma Marstacimab Pharmacokinetic Parameters Following Multiple Doses

Parameter (Unit) ^a	PF-06741086 300 mg SC Loading + 150 mg SC QW Non-Inhibitor ^c (N=6)	PF-06741086 300 mg SC QW Non-Inhibitor (N=7)	PF-06741086 450 mg SC QW Non-Inhibitor (N=6)	PF-06741086 300 mg SC QW Inhibitor (N=7)	Overall - PF-06741086 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_{τ} (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)
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)

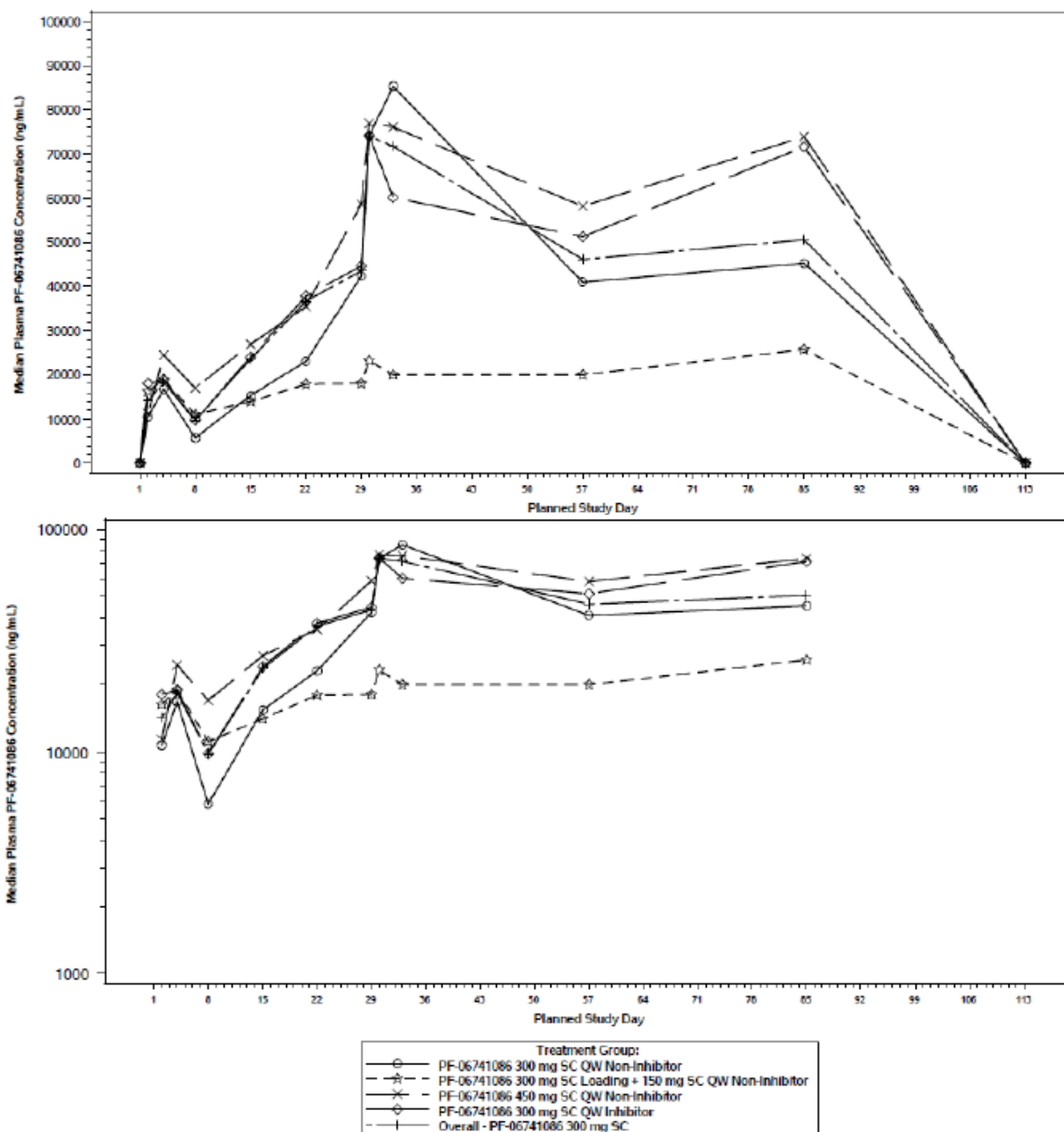
Source: Table 12, page 59 of Study B7841002 CSR

^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.

Abbreviations: %CV, percent coefficient of variation; AUC_{last} , area under the concentration-time profile from time 0 to the time of the last quantifiable concentration; AUC_{τ} , area under the concentration-time profile from time 0 to time tau, the dosing interval; CL/F, apparent clearance; $C_{\max}$, maximum plasma concentration; $C_{\min}$, lowest concentration observed during dosing interval; CSR, clinical study report; N, total number of participants in the treatment group; n, number of participants contributing to the summary statistics; QW, once weekly; SC, subcutaneous, $T_{\max}$, time to reach maximum concentration

Figure 25. Median Plasma Marstacimab Concentration-Time Profile, Linear (Top) and Semi-Logarithmic (Bottom) Scales

Source: Figure 2, page 58 of Study B7841002 CSR

Note: The dose of one 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 noninhibitor dose cohort. Pharmacokinetic concentrations for four participants (one subject from the marstacimab 300 mg SC QW noninhibitor dose cohort, two participants from the marstacimab 450 mg SC QW noninhibitor dose cohort and one 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.

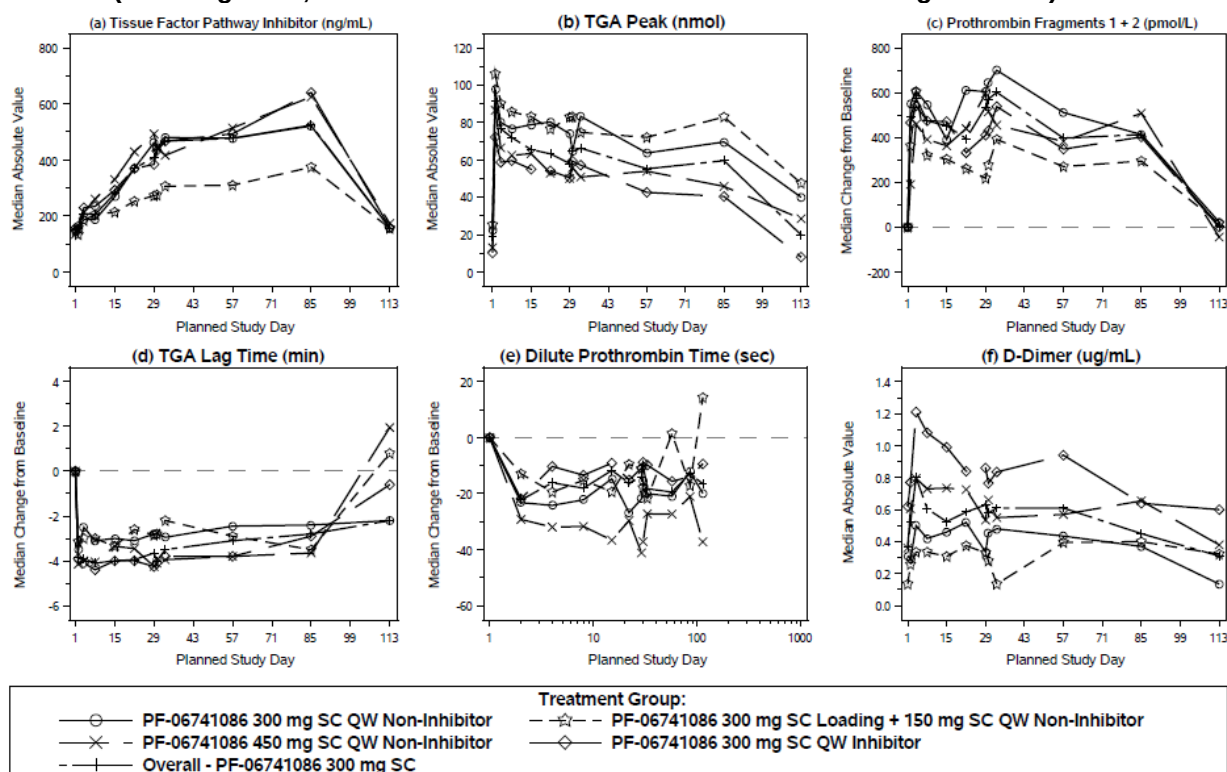
Abbreviations: CSR, clinical study report; QW, weekly; SC, subcutaneous

Treatment related changes in PD parameters were also evaluated. The median absolute values (TFPI, peak TGA and D-dimer) or median changes from baseline (TGA lag time, diluted prothrombin time and prothrombin fragment 1+2) versus time are provided in [Figure 26](#). The

HYMPAVZI (marstacimab-hncq) injection

total TFPI increased with increase in dose, consistent with the binding of free TFPI with marstacimab, resulting in delayed elimination of bound TFPI. For other PD parameters, although response to treatment was observed (e.g., increase in TGA peak, prothrombin fragments 1+2, D-dimer and decrease in TGA lag time, diluted prothrombin time) there was no consistent dose-related effect observed and variability was high.

Figure 26. Median Absolute Values (TFPI, Peak TGA and D-Dimer) or Median Changes From Baseline (TGA Lag Time, Diluted Prothrombin Time and Prothrombin Fragment 1+2) vs. Time



Source: Figure 14.5.7.4, page 471 of Study B7841002 CSR

Note: The dose of one participant was modified from 450 mg to 300 mg due to multiple severe injection site reactions.

Abbreviations: CSR, clinical study report; QW, weekly; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; TGA, thrombin generation assay

We concluded as there were no consistent dose-dependent changes observed in PD parameters, especially peak thrombin generation, PD changes were not considered when evaluating the dose selection. Evaluation of Study B7841002 for Phase 3 dose selection is provided in Section 6.1.

A total of three participants had treatment-induced ADA (11.5%, 3/26). Among the three participants, no participant tested positive for neutralizing antibody (NAb).

Study B7841009

A Phase 1, open-label, randomized, 4-period, 2-sequence, crossover study to evaluate the bioequivalence of marstacimab (PF-06741086) PFS device and PFP device following subcutaneous administration in healthy adult male participants.

Primary Objective

To compare the single dose PK of marstacimab (300 mg) administered subcutaneously with a PFP device to that with the PFS device in healthy adult male participants.

Study Design

This was a Phase 1, open-label, randomized, single dose, 4-period, 2-sequence, fully replicate crossover study in healthy adult male participants. A single dose of 300 mg marstacimab (given as two single injections of 150 mg) was administered subcutaneously into the abdomen on Day 1 of each period, following a standardized breakfast. Dose administration in each of the four period was alternated between the top half and bottom half of the abdomen. The pharmacokinetic sampling was conducted at predose, and 1, 2, 4, 8, 12, 24, 48, 72 hours, and 7, 14, 21 days after dosing. The immunogenicity samples were collected at predose (on Day 1 prior to dosing) and on Day 21.

Results

The study was terminated early due to a serious adverse event (SAE) of pulmonary embolism in one participant. A total of 18 participants completed at least 1 period and contributed to data for calculation of PK parameters. Summary of mean plasma PK parameters and statistical comparison of PFS and PFP are provided in [Table 84](#) and [Table 85](#). The plasma concentration versus time curve is shown in [Figure 27](#). The ratios (90% CI) of geometric means of C_{max} and AUC_{last} were 104.1% (93.7 to 115.6%) and 107.5% (95.2 to 121.4%) showing comparable exposure when administered via PFP and PFS. The median time to reach maximum concentration was 72 hours for both PFP and PFS with overlapping range of 60 to 146 hours. As the sample size was smaller than planned, a sensitivity analysis was conducted using data from participants who completed at least 2 periods (N=15). The results showed that the geometric mean ratios of C_{max} and AUC_{last} were still comparable (C_{max} : 107.7% [98.8 to 117.5%] and AUC: 111.9% [101.1 to 123.9%]). A total of six participants tested positive for ADAs and of those, two participants positive for NAb.

Table 84. Summary of Plasma Marstacimab Pharmacokinetic Parameters Administered via PFP vs. PFS

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: Table 10, page 29 of Study B7841009 CSR

^a Geometric mean (geometric %CV) for all except median (range) for T_{max} and arithmetic mean±standard deviation for t_{1/2}. Abbreviations: %CV, percent coefficient of variation; AUC_{inf}, area under the concentration-time profile from time 0 extrapolated to infinite time; AUC_{last}, area under the concentration-time profile from time 0 to the time of the last quantifiable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CSR, clinical study report; 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; F, PFP, prefilled pen; PFS, prefilled syringe; T_{max}, time to reach maximum concentration; t_{1/2}, elimination half-life; V_Z/F, apparent volume of distribution

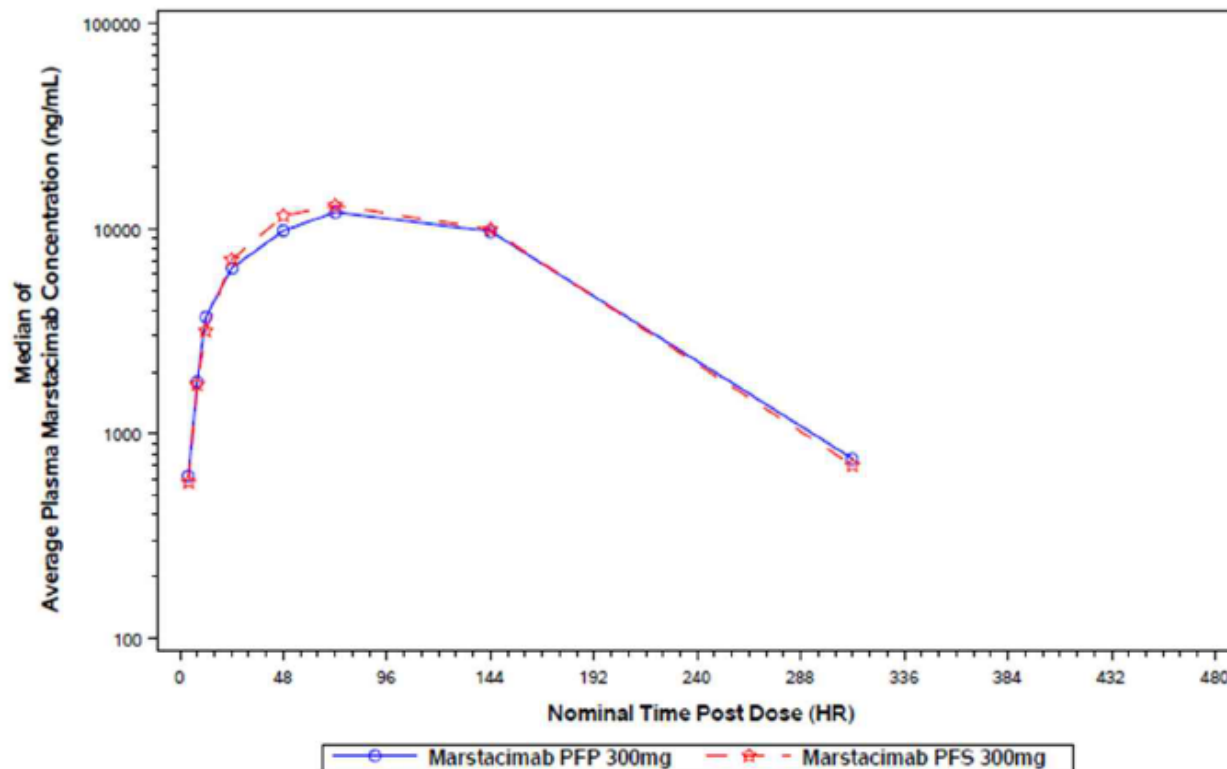
Table 85. Statistical Comparison of Marstacimab Pharmacokinetic Parameters Administered via PFP vs. PFS

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 11, page 29 of Study B7841009 CSR

Natural log-transformed AUC_{last} and C_{max} were analyzed using a mixed effect model with sequence, period, treatment as fixed effects. Values had been back-transformed from the log scale.

Abbreviations: AUC_{last}, area under the concentration-time profile from time 0 to the time of the last quantifiable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CSR, clinical study report; N, total number of participants who completed all 4 periods; PFP, prefilled pen; PFS, prefilled syringe

Figure 27. Median Plasma Marstacimab Concentration-Time Profile Following Administration of PFP vs. PFS (Semi-Logarithmic Scale)

Source: Figure 1, page 28 of Study B7841009 CSR

Abbreviations: CSR, clinical study report; PFP, prefilled pen; PFS, prefilled syringe

Study B7841010

A Phase 1, single-arm, open-label, nonrandomized, noncontrolled multicenter study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of a single subcutaneous dose of PF-06741086 in Chinese adult participants with severe hemophilia.

Primary Objective

To determine the safety and tolerability of a single SC dose of marstacimab administered to Chinese adult participants with severe hemophilia A or B with or without inhibitors.

Study Design

This study was a single-arm, open-label, nonrandomized, noncontrolled, multicenter study in Chinese adult participants between ages 18 to <75 years with severe hemophilia A or B, with or without inhibitor. All participants (N=6) received a single subcutaneous injection of marstacimab 300 mg (2 x 150 mg) on Day 1. The pharmacokinetic and PD blood samples were collected at predose and 1, 4, 12, 24, 48, 72 hours and 14, 21, 28 days postdose. The immunogenicity samples were collected at predose and Days 14, 21, and 28 of the study.

Results

Summary of plasma marstacimab PK parameters are provided in [Table 86](#). Median plasma marstacimab concentration-time profile is shown in [Figure 28](#). Treatment-related changes were observed in all PD markers (i.e., increase in total TFPI, prothrombin fragment 1+2, d-dimer, TGA peak and decrease in dPT and TGA lag time). Two participants had tested positive for ADA but negative for NAb.

Table 86. Summary of Plasma Marstacimab Pharmacokinetic Parameters in Chinese Participants

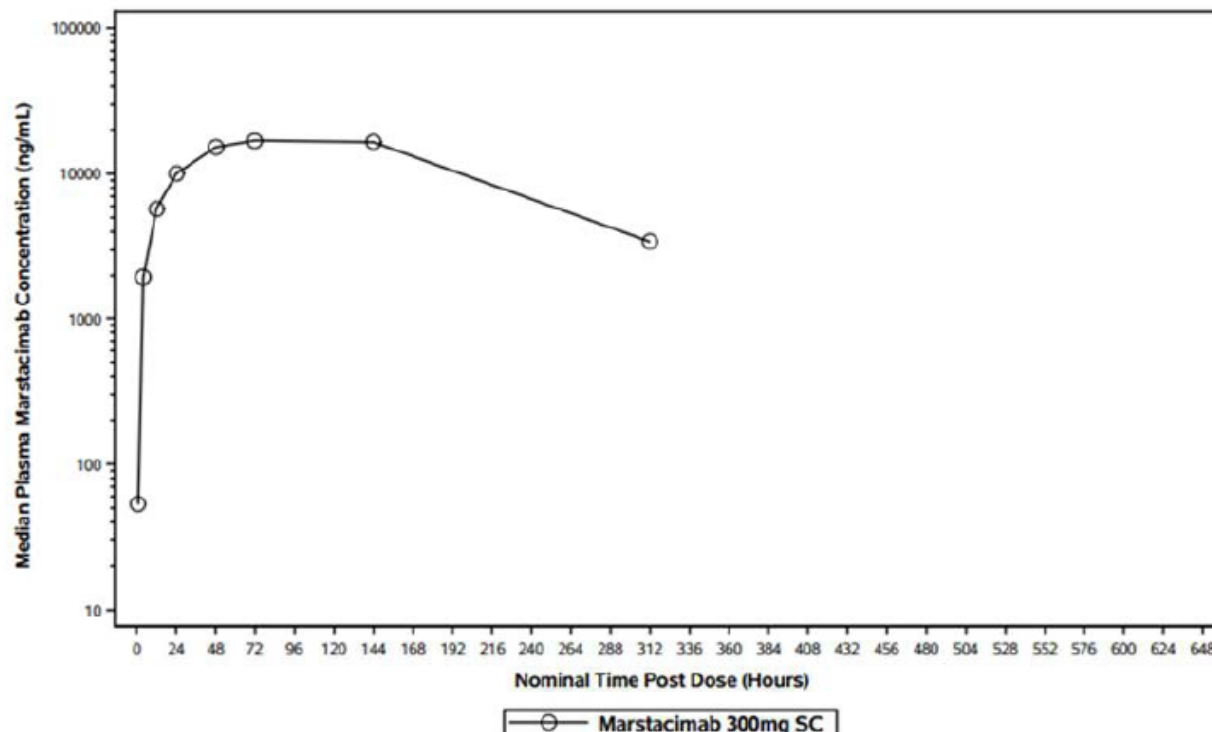
Parameter (Unit) ^{a, b}	Marstacimab 300mg SC (N=6)
N2, N3	6, 4
AUC _{inf} (ng.hr/mL)	4549000 (7)
AUC _{last} (ng.hr/mL)	2917000 (60)
C _{max} (ng/mL)	15610 (35)
T _{max} (hr)	73.15 (71.9 - 167)
t _{1/2} (hr)	90.48 ± 26.025
CL/F (L/hr)	0.06595 (7)
V _z /F (L)	8.305 (29)

Source: Table 12, page 34 of Study B7841010 CSR

^a Geometric mean (geometric %CV) 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.

Abbreviations: AUC_{inf}, area under the concentration-time profile from time 0 to extrapolated to infinite time; AUC_{last}, area under the concentration-time profile from time 0 to the time of the last quantifiable concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CSR, clinical study report; N, total number of patients in the treatment group in the indicated population; N2, number of patients contributing to the summary statistics; N3, number of patients contributing to the summary statistics for t_{1/2}, AUC_{inf}, V_z/F, and CL/F; SC, subcutaneous; T_{max}, time to reach maximum concentration; t_{1/2}, elimination half-life; V_z/F, apparent volume of distribution

Figure 28. Median Plasma Marstacimab Concentration-Time Profile in Chinese Participants (Semi-Logarithmic Scale)

Source: Figure 1, page 33 of Study B7841010 CSR
 Abbreviations: CSR, clinical study report; SC, subcutaneous

14.3. Bioanalytical Method Validation and Performance

14.3.1. Bioanalytical Method for PK Assessment

Plasma marstacimab concentrations were assayed using a validated electrochemiluminescence (ECL) method. Standards, controls, and test samples were incubated with TFPI (1.0 µg/mL), which has been immobilized on a 96-well MSD standard plate. After incubation, unbound material is washed away and marstacimab bound to the plate is incubated with a primary detection antibody, Mu anti-TFPI Ab. Following incubation, the plate is washed and bound marstacimab is incubated with a secondary detection antibody, goat anti-mouse IgG Sulfo TAG (1.0 µg/mL). After a final wash, 2X read buffer containing tripropylamine is added immediately prior to reading the plate on an MSD Sector Imager 600 plate reader generating a chemiluminescent signal. The signal is directly proportional to the amount of marstacimab in the sample.

An overview of marstacimab ECL method validation parameters and assay performance are provided in [Table 87](#) and [Table 88](#). For all clinical studies, 2 ECL methods were developed and validated (i.e., method (b) (4) 15-1536 for Studies B7841001, B7841002, B7841003, B7841005, B7841007 and B7841009 and method (b) (4) P7615MVHuP1AP for Study B7841005 and

HYMPAVZI (marstacimab-hncq) injection

B7841010). The Applicant provided cross validation results that demonstrated equivalency of the two methods. The method validation and sample analysis are deemed adequate.

Table 87. Marstacimab Bioanalytical Method Validation, Study (b) (4) 15-1536

Bioanalytical method validation report name, amendments and hyperlinks	Module 5.3.1.4 Original QPS Report 15-1536 : Bioanalytical Method Validation Report: The Validation of an ECL Assay Method for the Determination of PF-06741086 in Sodium Citrate Human Plasma Module 5.3.1.4 15-1536 Amendment 1 : Amended Bioanalytical Method Validation Report: The Validation of an ECL Assay Method for the Determination of PF-06741086 in Sodium Citrate Human Plasma Module 5.3.1.4 15-1536 Amendment 2 : Amended Bioanalytical Method Validation Report: The Validation of an ECL Assay Method for the Determination of PF-06741086 in Sodium Citrate Human Plasma		
Method description	A validated sandwich format using TFPI as capture and Mu anti-TFPI Ab antibody followed by sulfo-tag labeled goat anti-mouse antibody as detection		
Materials used for standard calibration curve and concentration	Marstacimab (PF-06741086), lot 15-001718, expiration date 21Jul2017, 100 mg/mL		
Validated assay range	100 ng/mL to 1,000 ng/mL in undiluted sodium citrate human plasma		
Material used for QC's and concentration	Marstacimab (PF-06741086), lot 15-001718, expiration date 21Jul2017, 100 mg/mL		
Minimum required dilutions (MRDs)	1:100		
Source and lot of reagents	Capture/Coat, TFPI, 1.51 mg/mL, Lot# PRB04711, (b) (4) Detection Ab 1, Mu anti-TFPI Ab, 2.6 mg/mL, Lot# PAB3581 (b) (4) Detection Ab 2, Sulfo-tag labeled Anti-Mouse Antibody (Goat), 0.5 mg/mL, Lot varies, (b) (4)		
Regression model and weighting	5-Parameter logistic (5PL), 1/Y ²		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 3
	Cumulative accuracy (%bias)* from LLOQ to ULOQ	-3.3 to 41.3%	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 3
	Cumulative precision (%CV) from LLOQ to ULOQ	1.6 to 4.7%	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 3
Performance of QC's during accuracy and precision runs	Cumulative accuracy (%bias)* in 5 QC's (LLOQ, Low, Medium, High, and ULOQ)	-2.4 to 7.0%	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 4
	Inter-batch %CV	3.4 to 6.8%	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 4
	Total Error (TE)	Not Calculated	
Selectivity and matrix effect	Normal Healthy Plasma: Unspiked: 10/10 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 10/10 individual lots were ±25% accuracy		Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 10

HYMPAVZI (marstacimab-hncq) injection

	ULOQ (1000 ng/mL) spike: 10/10 individual lots were $\pm 25\%$ accuracy Diseased Plasma: Unspiked: 10/10 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 8/10 individual lots were $\pm 25\%$ accuracy ULOQ (1000 ng/mL) spike: 10/10 individual lots were $\pm 25\%$ accuracy	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 11
Interference and specificity	Target (TFPI): No target interference observed up to and including 200 ng/mL of TFPI at both LLOQ and ULOQ ADA (Rb Anti-TFPI Ab): ADA interference observed at 250 ng/mL of Rb Anti-TFPI Ab at LLOQ No ADA interference observed up to and including 1000 ng/mL of Rb Anti-TFPI Ab at ULOQ	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 13
Hemolysis effect	Unspiked: 6/6 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 6/6 individual lots were $\pm 25\%$ accuracy ULOQ (1000 ng/mL) spike: 6/6 individual lots were $\pm 25\%$ accuracy	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 12
Lipemic effect	Unspiked: 6/6 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 5/6 individual lots were $\pm 25\%$ accuracy ULOQ (1000 ng/mL) spike: 6/6 individual lots were $\pm 25\%$ accuracy	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 12
Dilution Linearity and hook effect	Dilution linearity was tested by spiking marstacimab (PF-06741086) stock standard into normal human plasma at a concentration of 250,000 ng/mL. The sample was diluted 1:50, 1:100, 1:250, 1:500 and 1:1000. Cumulative %CV was 7.7% and cumulative accuracy was 3.2% for all concentrations that fell within the range of quantitation. Hook effect was not examined.	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 6
Bench-top/process stability	72 hours in human plasma at ambient temperature	Module 5.3.1.4 (b) (4) Report 15-1536 Amendment 2 Table 7b
Freeze-Thaw stability	5 Freeze-Thaw cycles stability established at -20°C 7 Freeze-Thaw cycles stability established at -70°C	Module 5.3.1.4 Original (b) (4) Report 15-1536 Table 9a & 9b
Long-term storage stability	545 Days at -70°C and -20°C established	Module 5.3.1.4 (b) (4) Report 15-1536 Amendment 1 Table 8b; Table 8d
Parallelism	N/A	
Carryover	N/A	

Source: Summary of biopharmaceutical studies and associated analytical methods Table 15

Note: the upper range of cumulative accuracy for calibration curve stated as 41.3% is due to a calculation error. The Applicant clarified that the correct calculation is 13.0% (Response to information request received March 15, 2024).

^a Bias refers to %RE (relative error)

Abbreviations: %CV, coefficient of variance; Ab, antibody; ADA, antidrug antibodies; BQL, below the limit of quantification; ECL, electrochemiluminescence; LLOQ, lower limit of quantification; MRD, minimum required dilution; N/A, not applicable; QC, quality check; TE, total error; TFPI, tissue factor pathway inhibitor; ULOQ, upper limit of quantification

Table 88. Marstacimab Bioanalytical Method Validation, Study (b) (4) P7615MVHuP1AP

Bioanalytical method validation report name, amendments and hyperlinks	Module 5.3.1.4 Original UPP Report P7615MVHuP1: Bioanalytical Method Full Validation Report: The Validation of an Electrochemiluminescence (ECL) Method for the Determination of PF-06741086 in Human Sodium Citrate Human Plasma Module 5.3.1.4 P7615MVHuP1 Amendment 1: Amended Bioanalytical Method Full Validation Report: The Validation of an Electrochemiluminescence (ECL) Method for the Determination of PF-06741086 in Human Sodium Citrate Human Plasma		
Method description	A validated sandwich format using TFPI as capture and Mu anti-TFPI Ab antibody followed by sulfo-tag labeled goat anti-mouse antibody as detection		
Materials used for standard calibration curve and concentration	Marstacimab (PF-06741086), lot 128926-82-RS, expiration date 31Oct2021, 10.1 mg/mL		
Validated assay range	100 ng/mL to 1,000 ng/mL in undiluted human sodium citrate plasma		
Material used for QCs and concentration	Marstacimab (PF-06741086), lot 128926-82-RS, expiration date 31Oct2021, 10.1 mg/mL		
Minimum required dilutions (MRDs)	1:100		
Source and lot of reagents	Capture/Coat, TFPI, 1.0 mg/mL, Lot# PRB005679, Pfizer, Address Detection Ab 1, Mu anti-TFPI Ab, 2.6 mg/mL, Lot# PAB3581, (b) (4) Detection Ab 2, Sulfo-tag labeled Anti-Mouse Antibody (Goat), 0.5 mg/mL, Lot varies. (b) (4)		
Regression model and weighting	5-Parameter logistic (Marquardt), 1/Y ²		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 3
	Cumulative accuracy (%bias)* from LLOQ to ULOQ	-2.8 to 3.0%	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 3
	Cumulative precision (%CV) from LLOQ to ULOQ	3.0 to 6.3%	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 3
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs (LLOQ, Low, Medium, High, and ULOQ)	-6.2 to 1.0%	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 4
	Inter-batch %CV	8.3 to 15.8%	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 4
	Total Error (TE)	9.9 to 16.8%	Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 4
Selectivity and matrix effect	Normal Healthy Plasma: Unspiked: 9/10 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 8/10 individual lots were ±25% accuracy ULOQ (1000 ng/mL) spike: 10/10 individual lots were ±25% accuracy		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 6
	Diseased Plasma: Unspiked: 10/10 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 10/10 individual lots were ±25% accuracy ULOQ (1000 ng/mL) spike: 10/10 individual lots were ±25% accuracy		Module 5.3.1.4 Amendment 1 (b) (4) Report P7615MVHuP1 Table 24
Interference and specificity	Target (TFPI): No target interference observed up to and including 200 ng/mL of TFPI at both LLOQ and ULOQ ADA (Mouse anti-TFPI Ab): No ADA interference observed up to and including 1000 ng/mL of Mu Anti-TFPI Ab at both LLOQ and ULOQ		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 7-8
Hemolysis effect	Unspiked: 6/6 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 6/6 individual lots were ±25% accuracy ULOQ (1000 ng/mL) spike: 6/6 individual lots were ±25% accuracy		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 9
Lipemic effect	Unspiked: 6/6 individual lots passed (BQL) LLOQ (100 ng/mL) spike: 6/6 individual lots were ±25% accuracy ULOQ (1000 ng/mL) spike: 6/6 individual lots were ±25% accuracy		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 10
Dilution Linearity and hook effect	Dilution linearity was tested by spiking marstacimab (PF-06741086) stock standard into normal human plasma at a concentration of 250,000 ng/mL. The sample was diluted 1:50, 1:100, 1:250, 1:500, 1:1000 and 1:2000. A second dilution sample was prepared at a concentration of 10,000 ng/mL marstacimab and diluted 1:10 and 1:50. Combined %CV for both samples was 1.2 to 2.7% and combined accuracy was -4.8 to 1.0% for all concentrations that fell within the range of quantitation. Hook effect was not examined.		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 11
Bench-top/process stability	23 hours in human sodium citrate plasma at ambient temperature		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 13
Freeze-Thaw stability	7 Freeze-Thaw cycles stability established at -70°C and -20°C		Module 5.3.1.4 Original (b) (4) Report P7615MVHuP1 Table 15-16
Long-term storage stability	530 Days at -70°C and -20°C established		Module 5.3.1.4 Amendment 1 (b) (4) Report P7615MVHuP1 Table 25-26
Parallelism	Demonstrated in 6 individuals collected at ≥ 2 times (2x) of LOQ		Module 5.3.1.4 Amendment 1 (b) (4) Report P7615MVHuP1 Table 27
Carryover	N/A		N/A

Source: Summary of biopharmaceutical studies and associated analytical methods Table 16

Abbreviations: %CV, coefficient of variance; Ab, antibody; ADA, antidrug antibodies; BQL, below the limit of quantification; ECL, electrochemiluminescence; LLOQ, lower limit of quantification; LOQ, limit of quantification; MRD, minimum required dilution; N/A, not applicable; QC, quality check; TE, total error; TFPI, tissue factor pathway inhibitor; ULOQ, upper limit of quantification

14.3.2. Bioanalytical Method for PD Assessment

For PD characterization, plasma samples were analyzed for total TFPI, TGA (comprised of lag time, peak thrombin and endogenous thrombin generation potential), d-dimer, prothrombin fragment (PF) 1+2, dPT. All PD parameters were measured using laboratory developed test validated under CAP/CLIA requirements except for total TFPI, which was analyzed using validated bioanalytical method. Total TFPI, which includes marstacimab bound and unbound forms, was extracted from human plasma using a biotinylated noncompeting anti-TFPI antibody. This TFPI antibody complex was captured using streptavidin magnetic beads. Because TFPI is an endogenous component in human plasma, the method for TFPI quantitation was validated in mouse plasma as surrogate matrix.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

14.4.1. Summary of Clinical Studies

Immunogenicity of marstacimab was evaluated in three Phase 1 studies (Studies B7841009, B7841010, B7841001), two Phase 1/2 studies (Studies B7841002 and B7841003), and three Phase 3 studies (Studies B7841005, B7841007, B7841008). Among the Phase 3 studies, only Study B7841005 has available immunogenicity information, which is specifically from one of two subgroups, the noninhibitor subgroup because the study of inhibitor subgroup is still ongoing. Therefore, information in the draft label is coming from the noninhibitor cohort of the Phase 3 Study B7841005. The submitted clinical study results included participants who received 12-month treatment. [Table 89](#) contains the assessment of immunogenicity information up to 12 months for Study B7841005. Overall study design in terms of treatment duration and sampling time and size was adequate to assess the ADA impact on PK.

Table 89. Summary of Clinical Study Information and Immunogenicity Incidence

Study B7841005	Clinical Study Information
Dose regimen	150 mg SC once weekly (QW) with an initial loading dose of 300 mg SC
Treatment duration	12 months
Status	Inhibitor subgroup: completed (data available and assessments reported below) Noninhibitor subgroup: ongoing (data not available)
ADA incidence information	N (%)
Number of participants who received marstacimab	116
Applicant-reported ADA incidence	23/116 (19.8%)
Applicant-reported NAb incidence (among participants evaluated for ADA)	6/116 (5.2%)
FDA-calculated ADA incidence	23/116 (19.8%)
FDA-calculated NAb incidence (among ADA+)	6/23 (26%)

Source: Reviewer's analysis

Abbreviations: ADA, antidrug antibody; Nab, neutralizing antibody; PK, pharmacokinetic; QW, weekly; SC, subcutaneous

14.4.2. Highlight of Key Characteristics of Immunogenicity Assays Relevant to This Review

[Table 90](#) and [Table 91](#) show several assay characteristics of the ADA and NAb assay respectively, that are relevant for the analysis.

The ADA assay can detect 100 ng/mL of positive control in the presence of 25 µg/mL of marstacimab. A fraction (16%) of the ADA samples had drug concentration greater than the ADA drug tolerance (25 µg/mL). Therefore, the presence of marstacimab may interfere with detection of ADA in 16% of study samples.

The NAb assay can detect 1200 ng/mL of positive control in the presence of 50 µg/mL of marstacimab. A fraction (2.6%) of the NAb samples had drug concentration greater than the NAb drug tolerance of 50 mg/mL. Therefore, the presence of marstacimab may interfere with detection of NAb in 2.6% of study samples.

Table 90. Summary of Key ADA Assay Characteristics Related to Immunogenicity Assessment

Clinical Study Number	B7841005
Validation report number	(b) (4) 15-1919, Pfizer validation B7847007
Assay sensitivity	110 ng/mL
Drug tolerance	100 ng of PC was detected in the presence of 25 µg/mL of marstacimab
% of ADA samples with marstacimab concentration > drug tolerance (25 µg/mL)	16%

Source: Applicant's report (b) (4) 15-1919, recreated by the reviewer
Abbreviations: ADA, antidrug antibody; PC, positive control

Table 91. Summary of Key NAb Assay Characteristics Related to Immunogenicity Assessment

Clinical Study Number	B7841005
Validation report number	(b) (4) 15-1538, Pfizer Validation B7847004
NAb assay type	Ligand binding assay
Assay sensitivity	980 ng/mL
Drug tolerance	1200 ng of PC was detected in the presence of 50 µg/mL of marstacimab
% of NAb samples with marstacimab concentration > drug tolerance (50 µg/mL)	2.6%

Source: Applicant's report (b) (4) 15-1538, recreated by the reviewer.
Abbreviation: NAb, neutralizing antibody; PC, positive control

14.4.3. Methods for Evaluating the Effect of Immunogenicity on PK of Marstacimab

To evaluate the impact of immunogenicity on PK, the observed concentrations in two groups (ADA+ and ADA-) was compared with time-matched PK and ADA data using Immunogenicity Specimen (IS) tool developed in-house. At each timepoint, marstacimab geometric mean concentrations were tabulated by ADA+ and ADA- groups. For the statistical comparisons of concentration data between ADA+ and ADA- groups, the geometric mean ratio (GMR) of ADA+/ADA- and the corresponding 90% CI are presented.

This review does not include the evaluation of NAb effect on PK.

14.4.4. Effect of Immunogenicity on PK of Marstacimab – Results

The results of the IS analysis in Study B7841005, specifically, the effect of ADA on PK is presented. [Table 92](#) summarizes the marstacimab geometric mean concentrations in ADA+ and ADA- participants during the treatment period. The analysis of marstacimab concentration from ADA+ and ADA- samples during the treatment period and 90% confidence interval of GMR of drug concentration at each visit is provided in [Figure 29](#). Marstacimab concentration is lower in ADA+ participants. The IS analysis results show that the GMR (ADA+/ADA-) ranged from 0.50 to 0.76 through the study duration of 360 days. In addition, the 90% CI of the GMR is entirely below 1.0 at 6 of 8 time points over the study duration (i.e., except for Days 180 and 300). Therefore, development of ADA decreases the concentration of marstacimab.

Table 92. Summary of Geometric Mean Concentration by ADA Status at Each Study Visit

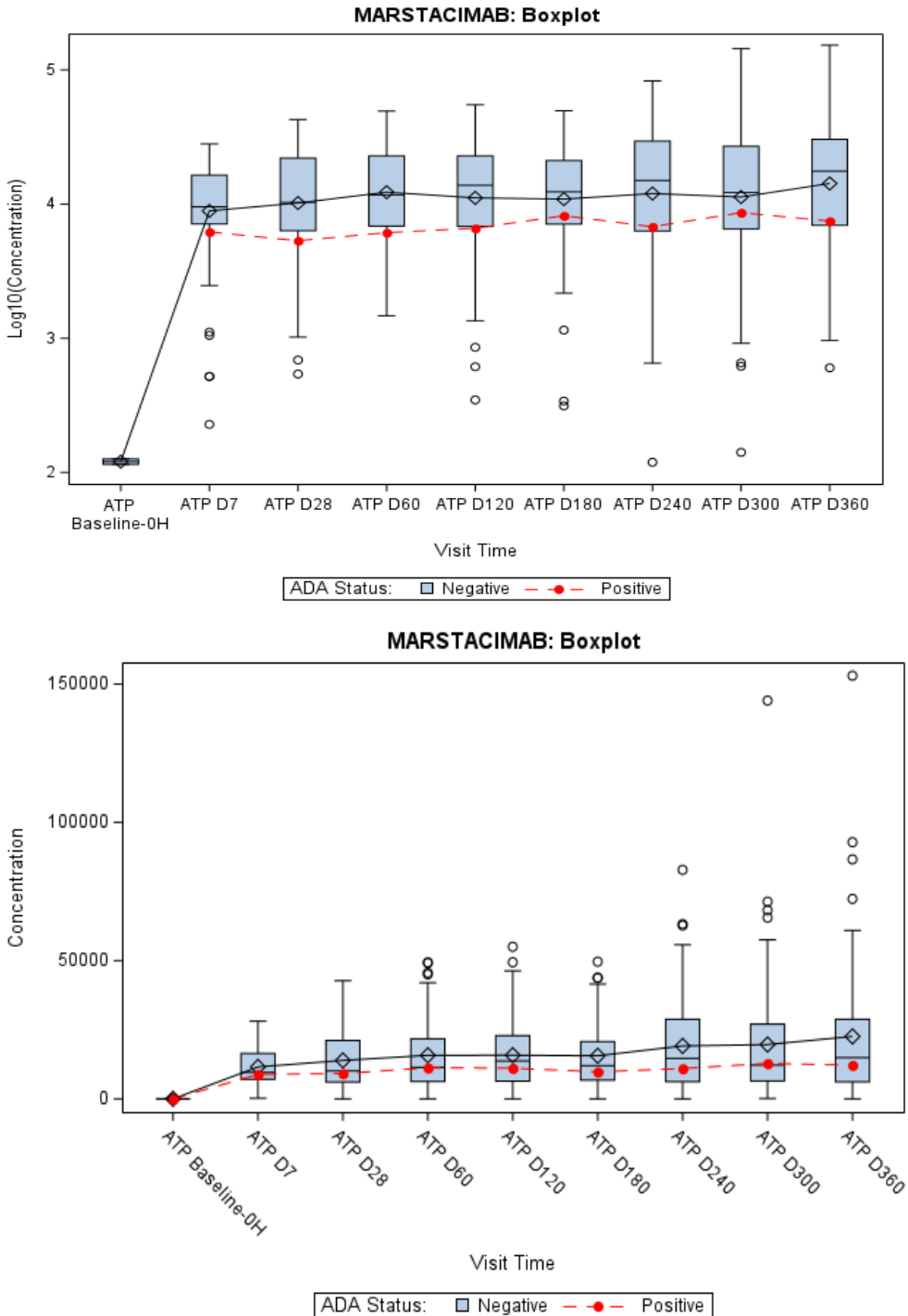
Arm	Treatment Duration (Day)	Total N	Marstacimab Geometric Mean Concentration (ng/mL)				GMR (90% CI) ADA+/ADA-
			ADA+ Group	N	ADA- Group	N	
Marstacimab	7	115	6197.91	23	8898.08	92	0.70 (0.49,0.99)
	28	115	5333.06	23	10185.67	92	0.52 (0.35,0.77)
	60	115	6120.97	23	12213.33	92	0.50 (0.34,0.74)
	120	111	6604.47	21	11121.01	90	0.59 (0.39,0.90)
	180	90	8190.22	21	10895.07	69	0.75 (0.49,1.16)
	240	109	6779.01	21	11981.04	88	0.57 (0.92,0.35)
	300	111	8633.15	21	11288.78	89	0.76 (0.47,1.25)
	360	102	7469.86	21	14239.95	81	0.52 (0.32,0.86)

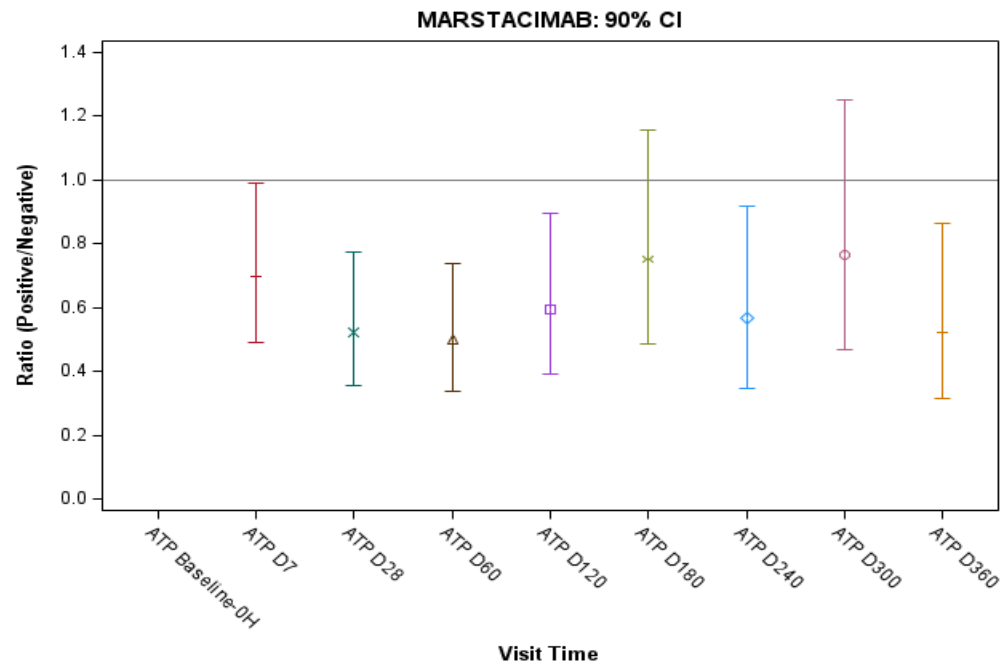
Source: Reviewer's analysis

Note – The nominal sampling days for ADA and PK did not fall on the day of dosing indicating that they were not predose samples (taken before the weekly dosing of marstacimab).

Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of participants; PK, pharmacokinetic(s)

Figure 29. Top and Middle Panels: Box Plot Analysis of Marstacimab Concentration in Logarithmic and Linear Scale From ADA+ and ADA- Samples During the 12-Month Treatment Period; Bottom Panel: 90% Confidence Interval of GMR of Drug Concentration at Each Visit





Source: Reviewer's analysis
Abbreviations: ADA, antidrug antibody; ATP, active treatment phase; CI, confidence interval; GMR, geometric mean ratio

14.4.5. Effect of Immunogenicity on Efficacy of Marstacimab

The impact of immunogenicity on efficacy of marstacimab was evaluated based on comparison of the clinical outcome (i.e., annualized bleeding rate [ABR]) in ADA+ and ADA- participants. The summary of the ABR of treated bleeds (primary endpoint) by ADA status is provided in [Table 93](#). Based on the results, the ADA impact on marstacimab PK did not affect clinical outcome. The mean ABR was 3.34 for ADA+ participants whereas the mean ABR was 4.92 in ADA- participants.

Table 93. Summary of the ABR of Treated Bleeds by ADA Status

Parameter	ADA+	ADA-
Number of participants	23	93
Mean ABR	3.34	4.92
Median ABR	2.02	2.02
Q1, Q3	1.01, 5.10	0.00, 5.09
Min, max	1.11, 19.5	0.00, 35.5

Source: Table 13 of Applicant's integrated summary of immunogenicity, recreated by the reviewer
Abbreviations: ABR, annualized bleeding rates; ADA, antidrug antibody; max, maximum; min, minimum; Q1, Q3, lower and upper quartile

14.5. Pharmacometrics Assessment

14.5.1. Summary of Applicant's Population PK and Pharmacodynamic Modeling Analyses

Both population pharmacokinetic (PPK) and pharmacodynamic (PKPD) modeling analyses were conducted to support the dose selection for adult and adolescent participants with hemophilia. The objectives of Applicant's modeling analysis were:

- To develop an integrated, predictive PPK model for marstacimab plasma drug and TFPI concentrations.
- To identify potential covariates which impact marstacimab concentration levels.
- To explore the relationship between free target (TFPI) and peak thrombin.

Method

NONMEM version 7.5.0 was used for all model estimations. Perl-speaks-NONMEM (PsN) version 5.3.0 was used for visual predictive check (VPC) and/or bootstrap simulations; R 4.1.3 was used for pre- and post-processing and for summarizing and plotting results. R package mrgsolve (version 1.0.4) was used for generating simulated PK and PKPD results. Marstacimab PK was described using a TMDD model defined in terms of clearance (CL), V_c , Q, V_p , first-order absorption rate constant (k_a), and absorption lag time (T_{lag}). Both drug concentration data and total receptor (TFPI) data were used to estimate model parameters. Separate residual error models were included in the model for PK and total TFPI. A PKPD model was developed to describe peak thrombin and its relationship to free TFPI predicted from the final PPK model using an E_{max} type of model. At all stages of model development, goodness-of-fit plots were examined to assess model adequacy, possible lack of fit, or violation of assumptions.

Results

The PPK model was developed based on all Phase 1 and 2 studies, and the Phase 3 Study B7841005 in participants with hemophilia A and B. The proposed dosing regimen (applied in Phase 3) is 300 mg marstacimab SC for a loading dose followed by 150 mg SC weekly (QW) maintenance dose. Meanwhile, individual participants who met protocol specified dose escalation criteria based upon breakthrough bleed were allowed to have the dose increased to 300 mg SC QW.

The PPK analysis was conducted using 2235 evaluable marstacimab concentrations in a total of 150 participants and 63 healthy participants. The summary of studies used for PPK analysis are listed in [Table 94](#). Covariate analysis identified the covariates in [Table 95](#) for the parameter estimates in the final model. In summary, the effect of population type (healthy versus hemophilia participants), ADA participant status (ADA positive versus ADA negative), hepatic function, race category (Asians versus non-Asians), renal impairment (normal versus mild renal impairment) and hemophilia type (hemophilia A versus hemophilia B) were estimated. Their

effect on pharmacokinetics of marstacimab was not considered significant after accounting for the weight-adjusted effect on CL.

Table 94. Total Number of Observations and Imputed Datapoints Used for PPK and PKPD Analysis

Variable	Statistic	B7841001	B7841001; B7841005 B7841002	B7841005 (Adol.)	B7841005 (Adults)	B7841009	B7841010	All Studies Com- bined	Healthy Partici- pants Studies	Hemophilia partici- pants Studies
PK	N _{obs}	334	378	127	630	706	60	2235	1040	1195
	BLQ (%)	123 (36.8)	29 (7.7)	3 (2.4)	10 (1.6)	190 (26.9)	15 (25)	370 (16.6)	313 (30.1)	57 (4.8)
Total TFPI	N _{obs}	397	401	124	609	0	66	1597	397	1200
	Imputed Observations (%)	0 (0)	1 (0.2)	1 (0.8)	1 (0.2)	0 (0)	0 (0)	3 (0.2)	0 (0)	3 (0.2)
peak thrombin	N _{obs}	397	403	111	552	0	66	1529	397	1132
	Imputed Observations (%)	0 (0)	0 (0)	3 (2.7)	18 (3.3)	0 (0)	0 (0)	21 (1.4)	0 (0)	21 (1.9)

Source: Population Modeling Analysis Report (PMAR-Amendment) – Table 4.

Baseline total TFPI and Baseline peak thrombin were imputed to the median values of total TFPI and peak thrombin of the respective study.

Abbreviations: BLQ, below the limit of quantification; N_{obs}, number observed; PK, pharmacokinetic(s); PPK, population pharmacokinetic; PKPD, pharmacokinetic/pharmacodynamic; TFPI, tissue factor pathway inhibitor

Table 95. Covariates Considered in the Final Model

Model Parameter	Covariate of Interest
Weight effect on Vc	Similar to base model, weight exponent on Vc was estimated
Weight effect on CL	Similar to base model, weight exponent on CL was estimated
Participant type effect on CL	Additional effect on CL for a healthy participant was estimated
Race effect on CL	Additional effect on CL for an Asian participant was estimated
ADA subject status effect on CL	Additional effect on CL for an ADA positive participant was estimated
Renal impairment effect on CL	Additional effect on CL for a mild renal impairment participant was estimated

Source: Population Modeling Analysis Report (PMAR- Amendment) – Table 10

Abbreviations: ADA, antidrug antibody; CL, clearance; PMAR, Population Modeling Analysis Report; V_c, central volume of distribution

The PK of marstacimab and TFPI were best characterized by a semi-mechanistic, two-compartment TMDD model with quasi-steady state approximation and additional nonlinear clearance of the drug in the model. Normalized weight was included as a structural covariate in the model. The final marstacimab PK model parameter estimates, and the corresponding 95% confidence intervals (CIs) are presented in [Table 96](#).

Table 96. Parameter Estimates of the Final Population Pharmacokinetic 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_{TFPI}^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

Source: Population Modeling Analysis Report (PMAR Amendment) – Table S1

Bootstrap estimates were obtained from a bootstrap run with N=1000 samples using a PsN bootstrap routine. %RSE is provided for population (theta) parameters, %CV is provided for IIV parameters. Some of the IIVs were fixed to 15%CV. Residual variability was calculated on PK and TFPI via an additive error model on the log-scale with a thetarized (fixed) sigma parameter.

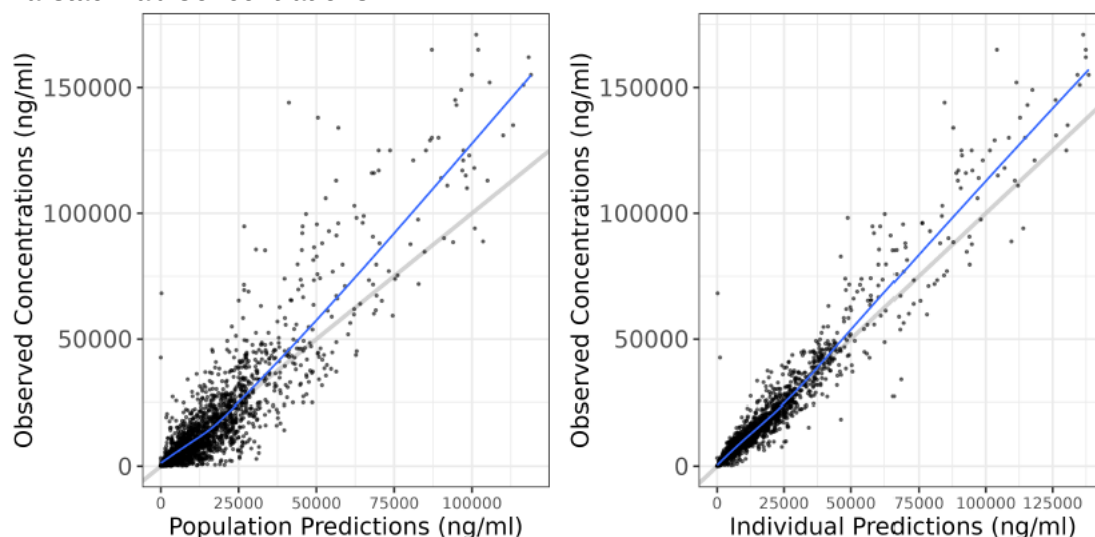
Abbreviations: %CV, coefficient of variation; ADA, antidrug antibody; CI, confidence interval; CL, clearance; F, bioavailability fraction; IIV, inter-individual variance; K_a , central compartment; K_{com} , drug-TFPI complex; K_{deg} , degradation rate; K_m , concentration of substrate which permits the enzyme to achieve half-maximum metabolic rate; KSS, quasi-steady state parameter; N, number of participants; PK, pharmacokinetic(s); PMAR, Population Modeling Analysis Report; PsN, Perl-speaks-NONMEM; Q, inter-compartmental flow; RSE, relative standard error; SE, standard error; TFPI, tissue factor pathway inhibitor; V_c , central volume; V_{max} , maximum volume; V_p , peripheral volume

The goodness-of-fit plots with population and individual predictions for the final marstacimab PK model are presented in [Figure 30](#). Residuals-based diagnostic plots of CWRES and IWRES versus PRED, IPRED and time after first dose (in days) are shown in [Figure 31](#) for drug concentrations, which do not show any systematic bias in the model after the first dose. The prediction-corrected VPC stratified by dosing regimen ([Figure 32](#)) illustrates the prediction percentiles and corresponding 95% CI of simulated concentrations overlaid on the observed

HYMPAVZI (marstacimab-hncq) injection

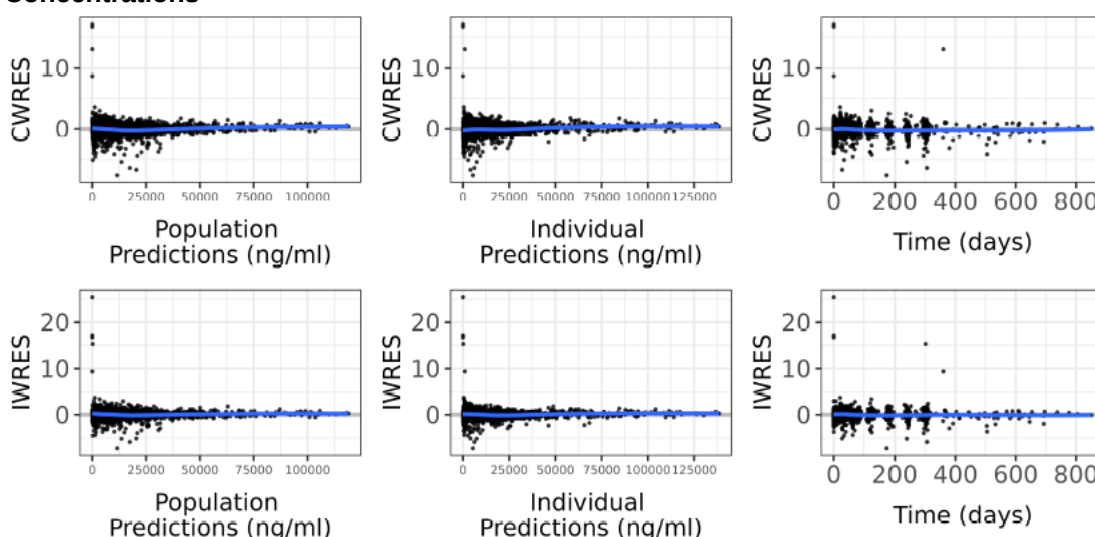
marstacimab concentrations and the corresponding 5th and 95th percentiles. Meanwhile, [Figure 33a](#) and [Figure 33b](#) show the VPC for the Phase 3 study (Study B7841005) only, divided by age group (adults and adolescents) and treatment group respectively. Overall, the diagnostic plots show the model is able to explain the observed marstacimab concentration from all clinical studies combined adequately.

Figure 30. Final Model Goodness-of-Fit Plots With Population and Individual Predictions for Marstacimab Concentrations



Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 11
Line of unity is shown in gray. Loess fit of data is shown in blue.

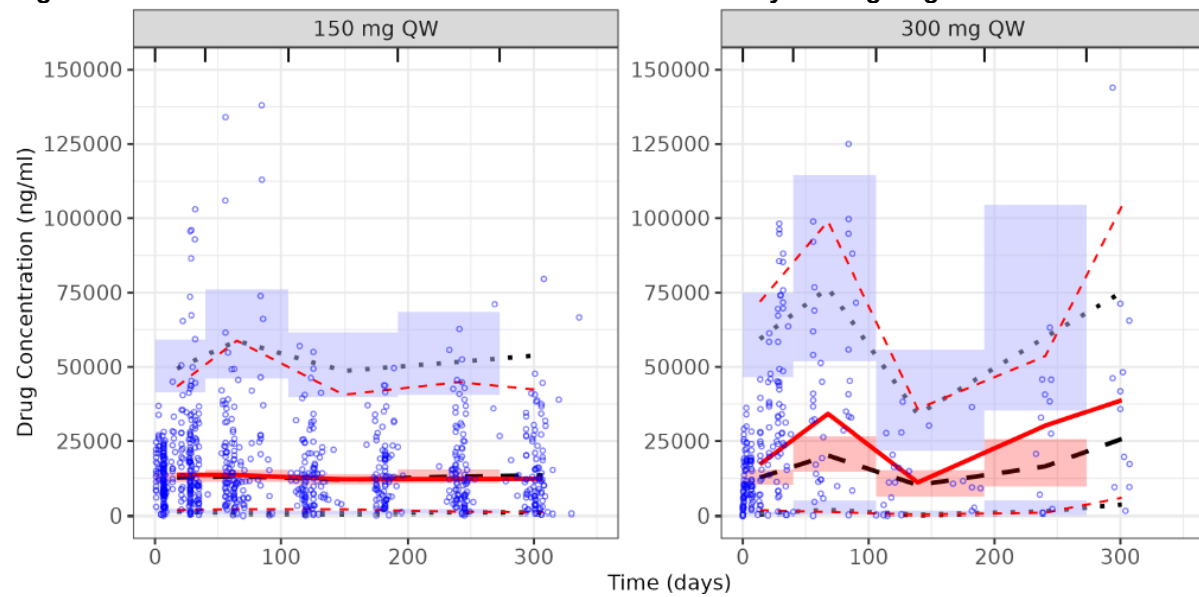
Figure 31. Final Model Residuals vs. Population, Individual Predictions for Marstacimab Concentrations



Source: Population Modeling Analysis Report (PMAR- Amendment) – Figure 12

Loess fit of residuals is shown in blue line.

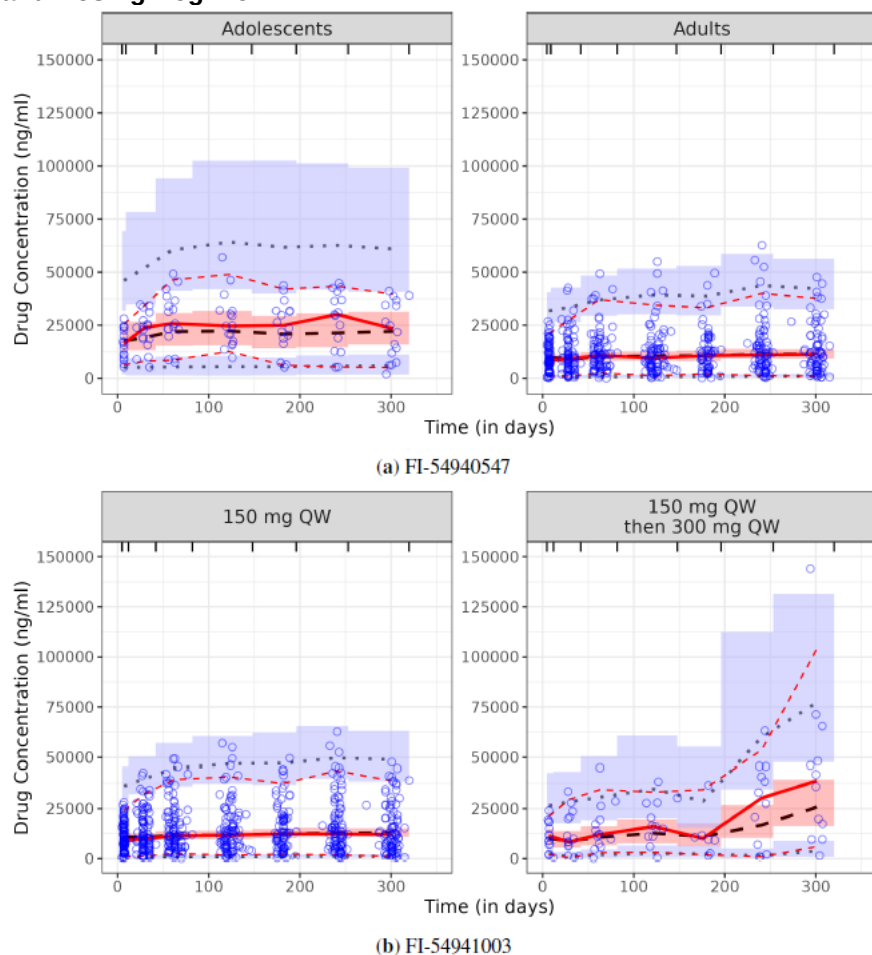
Abbreviations: CWRES, conditional weighted residuals; IWRES, individual weighted residuals

Figure 32. Final Model VPC of Marstacimab Concentration by Dosing Regimen

Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 13

VPC of drug concentration for all patients divided into 150 mg QW and 300 mg QW dosing regimen. The solid red line shows median of the observed data, the dashed black line shows the same for the simulated data. The pink-shaded region shows 90% prediction interval around the simulated median. The dotted black lines show 5th and 95th quantiles of the simulated data and the dashed red lines show the same for the observed data. The shaded blue regions show 90% prediction interval around 5th and 95th percentile of the simulated data. The blue circles show observed data.

Abbreviations: QW, once weekly; VPC, visual predictive check

Figure 33. Final Model VPC of Marstacimab Concentration for the Phase 3 Study by Age Group and Dosing Regimen

Source: Population Modeling Analysis Report (PMAR- Amendment) – Figure 14

Repository artifact IDs are shown in subfigure labels.

Figure 15a shows the VPC of drug concentrations from the B7841005 study only, stratified by adolescents' and adults' age groups. Figure 15b shows the same for the B7841005 study stratified by the dosing regimen, i.e., participants who received 150 mg dosing regimen and those who got escalated to the 300 mg dosing regimen. The solid red line shows median of the observed data, the dashed black line shows the same for the simulated data. The pink-shaded region shows 90% prediction interval around the simulated median. The dotted black lines show 5th and 95th quantiles of the simulated data and the dashed red lines show the same for the observed data. The shaded blue regions show 90% prediction interval around 5th and 95th percentile of the simulated data. The blue circles show observed data.

Abbreviations: ID, identification; QW, once weekly; VPC, visual predictive check

The final population PK model was used to calculate secondary PK parameters such as minimum concentration at steady state ($C_{\min,ss}$), maximum concentration at steady state ($C_{\max,ss}$), average concentration at steady state ($C_{\text{avg},ss}$), accumulation ratio, effective half-life ($t_{1/2}$) of marstacimab. A summary of these parameters is provided in [Table 97](#). The secondary parameters were calculated for all hemophilia participants studied in the program using the empirical Bayesian estimates of the model parameters from the final population PK model and simulating a dosing regimen of either 150 mg or 300 mg weekly dosing.

Table 97. Summary of Secondary Pharmacokinetic 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)

Source: Population Modeling Analysis Report (PMAR- Amendment) – Table 13

Abbreviations: %CV, coefficient of variation; ACCR, accumulation ratio; AUC_{ss}, area under the concentration-time curve at steady-state; $C_{avg,ss}$, average concentration at steady state; $C_{max,ss}$, maximum concentration at steady state; $C_{min,ss}$, minimum concentration at steady state; N, number of participants in the subgroup; $t_{1/2}$, elimination half-life

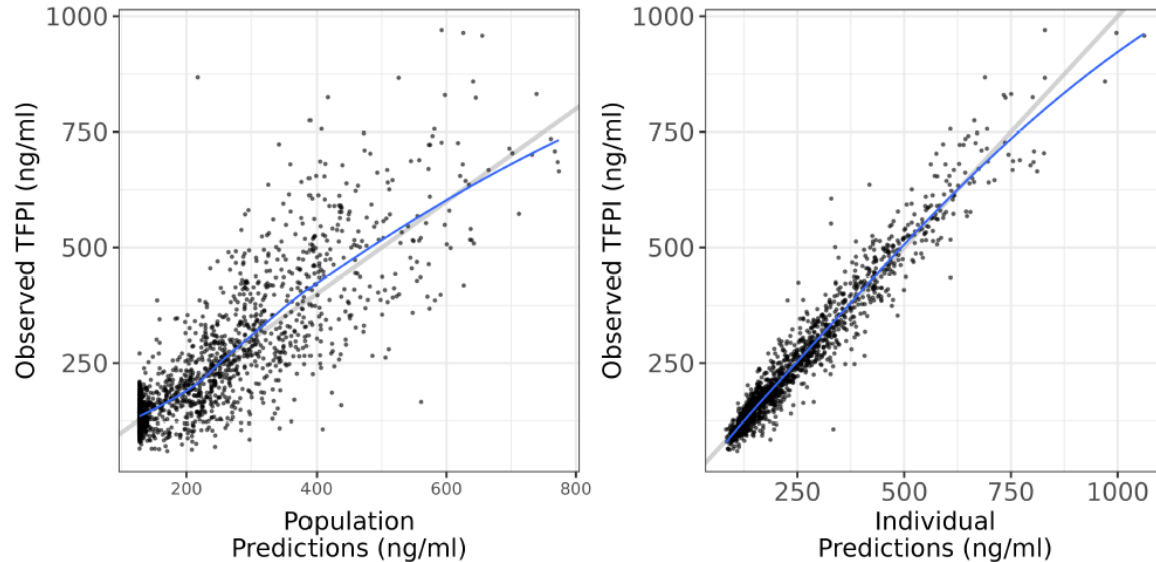
The review team found the Applicant's TMDD PPK model adequate to describe the marstacimab serum concentration-time profiles in the observed range following the administration of marstacimab in participants with hemophilia A and B from all clinical studies. The residual plots didn't indicate any obvious bias in the parameter estimates. Therefore, the PK model is acceptable for simulating post-hoc exposure metrics, e.g., $C_{avg,ss}$, $C_{max,ss}$, $C_{min,ss}$, and AUC_{ss} of marstacimab for exposure-response (E-R) analyses of efficacy or safety measurements.

Covariate analysis identified body weight as a significant covariate and applied to the clearance and volume distribution in the final PPK model. In addition, other covariates such as the effect of population type (healthy versus hemophilia patients), ADA participant status (ADA positive versus ADA negative), hepatic function, race category (Asians versus Non-Asians), renal impairment (normal versus mild renal impairment) and hemophilia type (hemophilia A versus hemophilia B) were not identified as significant covariates for the marstacimab exposure after accounting for the weight-adjusted effect on CL.

Similar to marstacimab concentration goodness of fit plots, there is good agreement between observed values and population/individual predictions from the model for total TFPI predictions. [Figure 34](#) shows a comparison of the observed total TFPI concentrations with population predictions (left panel) and individual predictions (right panel). Residuals-based diagnostic plots of CWRES and IWRES versus PRED, IPRED and time after first dose (in days) are shown in

[Figure 35](#) for total TFPI concentrations. Similarly, the residuals-based diagnostic plots do not show any systematic bias in the model with population or individual predictions and time after the first dose.

Figure 34. Final Model Goodness-of-Fit Plots With Population and Individual Predictions for TFPI Concentrations

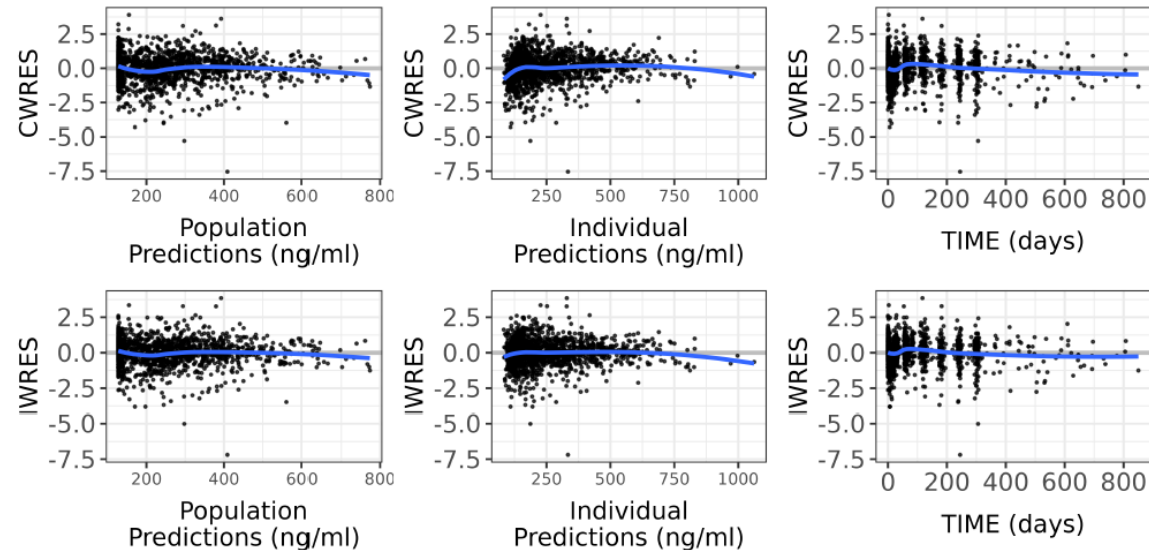


Source: Population Modeling Analysis Report (PMAR- Amendment) – Figure 17

Line of unity is shown in gray. Loess fit of data is shown in blue.

Abbreviation: TFPI, tissue factor pathway inhibitor

Figure 35. Final Model Residuals vs. Population, Individual Predictions for Total TFPI Concentrations



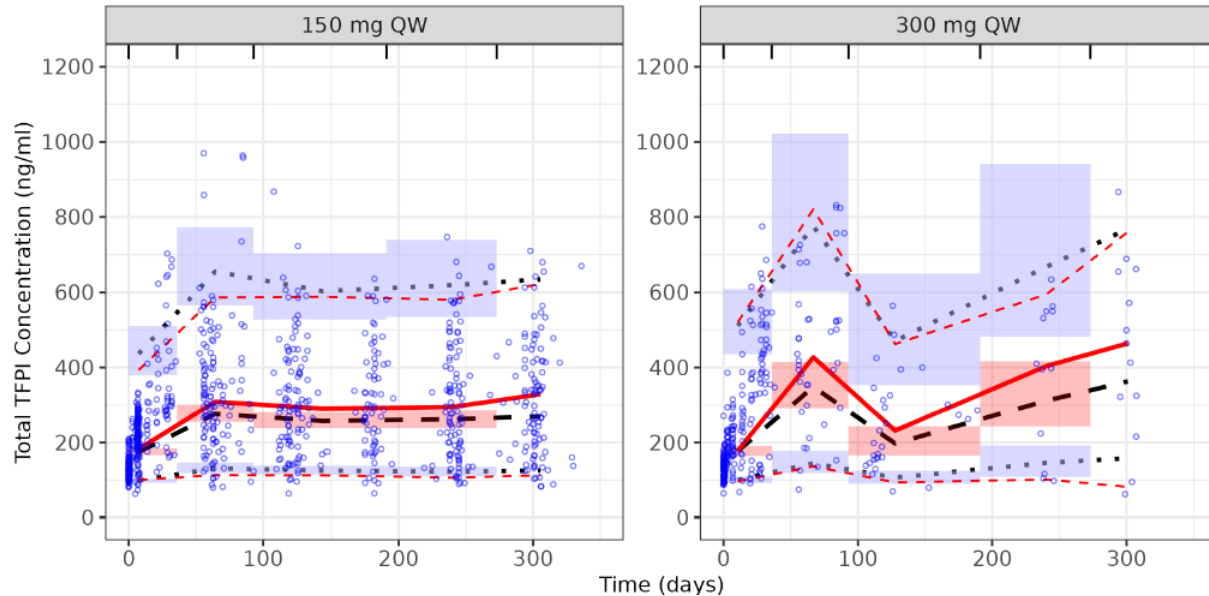
Source: Population Modeling Analysis Report (PMAR- Amendment) – Figure 18

Loess fit of residuals is shown in blue line.

Abbreviations: CWRES, conditional weighted residuals; IWRES, individual weighted residuals; TFPI, tissue factor pathway inhibitor

Figure 36 shows the VPC of total TFPI concentrations for all participants studied, stratified by dosing regimen type. Figure 37a and Figure 37b show the VPC for the Phase 3 study (Study B7841005) only, divided by age group (adults and adolescents) and treatment group respectively.

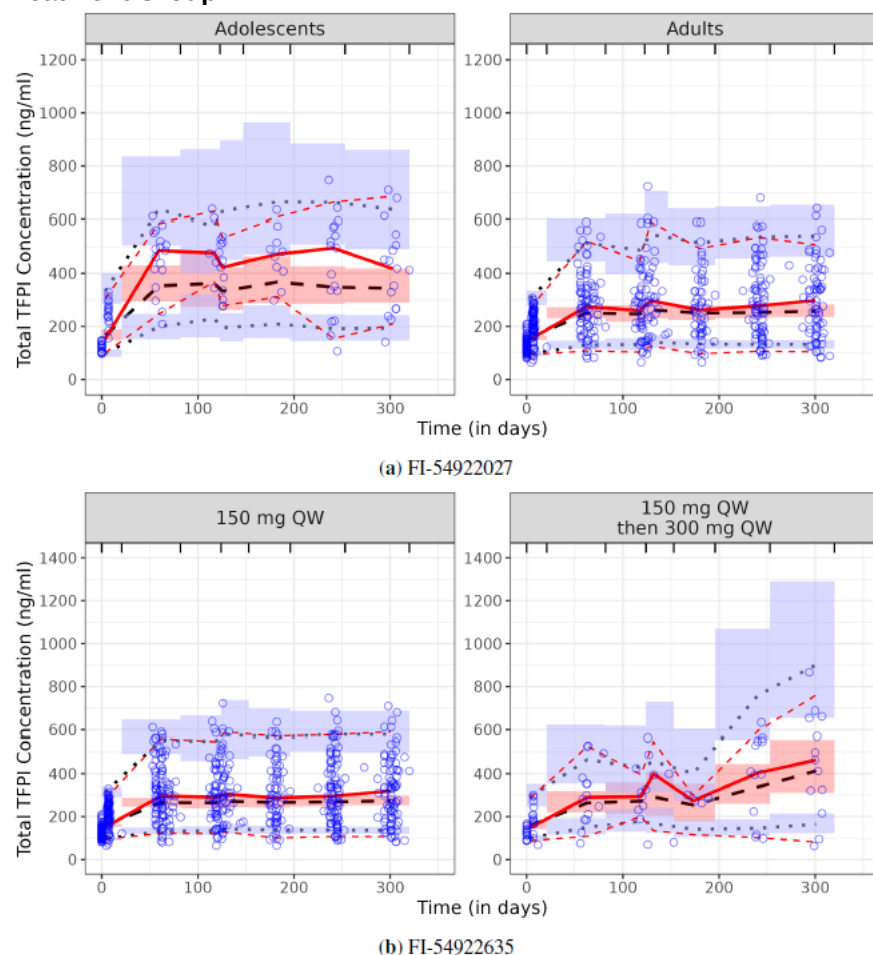
Figure 36. Final Model VPC of Total TFPI by Dosing Regimen



Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 19

The solid red line shows median of the observed data, the dashed black line shows the same for the simulated data. The pink-shaded region shows 90% prediction interval around the simulated median. The dotted black lines show 5% and 95% quantiles of the observed data and the dotted red line show the same for the simulated data. The shaded blue regions show 95% prediction interval around 5% and 95% of the simulated data. The blue circles show observed data.

Abbreviation: QW, once weekly; TFPI, tissue factor pathway inhibitor; VPC, visual predictive check

Figure 37. Final Model VPC of Total TFPI Concentrations for the Phase 3 Study by Age and Treatment Group

Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 20

Repository artifact IDs are shown in subfigure labels.

Figure 37a shows the VPC of total TFPI from the B7841005 study only, stratified by adolescents and adults age group. Figure 37b shows the same for the B7841005 study stratified by the dosing regimen, i.e., patients who received 150 mg and those who got escalated to the 300 mg dosing regimen. The solid red line shows median of the observed data, the dashed black line shows the same for the simulated data. The pink-shaded region shows 90% prediction interval around the simulated median. The dotted black lines show 5th and 95th quantiles of the simulated data and the dashed red lines show the same for the observed data. The shaded blue regions show 90% prediction interval around 5th and 95th percentile of the simulated data. The blue circles show observed data.

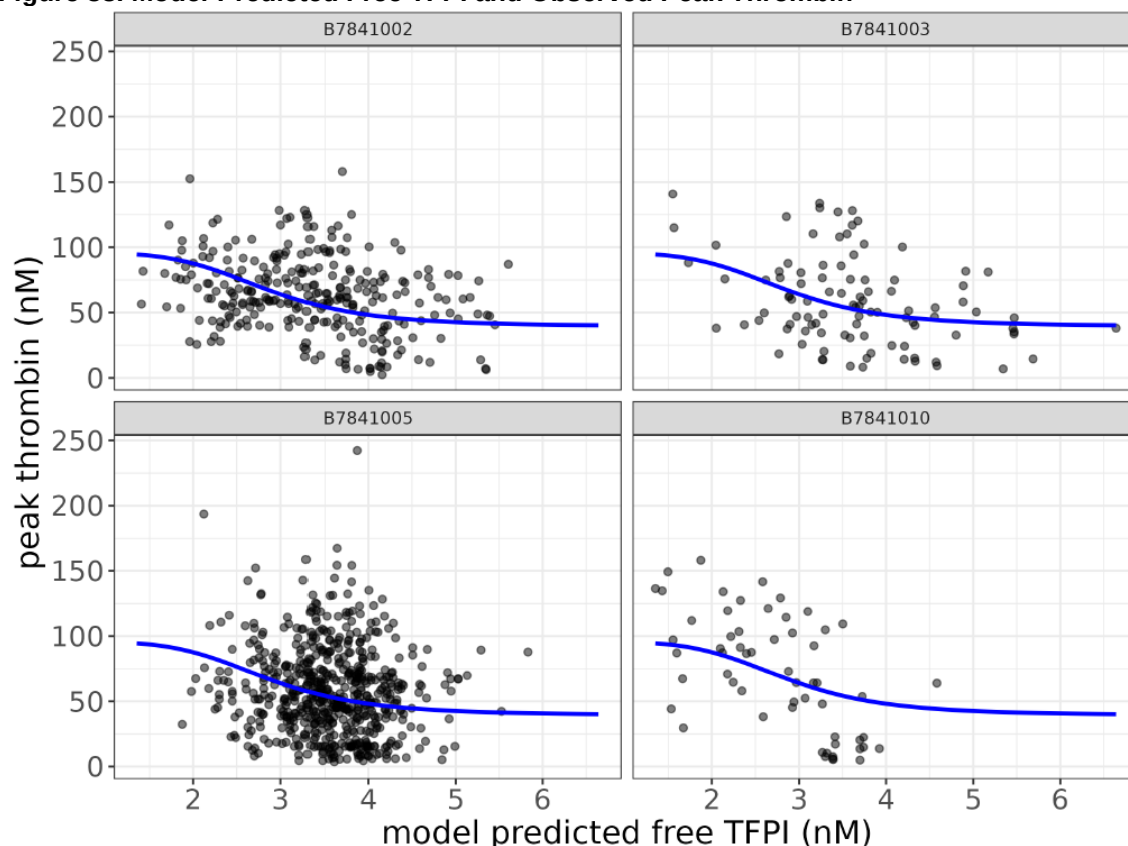
Abbreviation: ID, identification; QW, once weekly; TFPI, tissue factor pathway inhibitor; VPC, visual predictive check

As seen from above plots, total TFPI concentrations for the treatment group from all studies combined are described well by the model. But for the Phase 3 study, VPC plots showing the median total TPFI in adolescents was under predicted by the model, which indicates some limitation of using total TFPI in the next step of modeling analysis.

The PKPD model was developed based on all clinical studies in participants with hemophilia A and B. The total number of participants and samples used for PKPD analysis are listed in Table 94. The final population PK model was applied to calculate free TFPI for every individual (i.e., empirical Bayesian estimates). Model generated free TFPI was linked to peak thrombin using an $E_{\max}$ type of model with free TFPI as the independent variable and observed peak thrombin as the dependent variable. Figure 38 shows the relationship between observed peak thrombin and

the model calculated free TFPI for hemophilia participant population, which indicates an inhibitory relationship between free TFPI and peak thrombin.

Figure 38. Model-Predicted Free TFPI and Observed Peak Thrombin

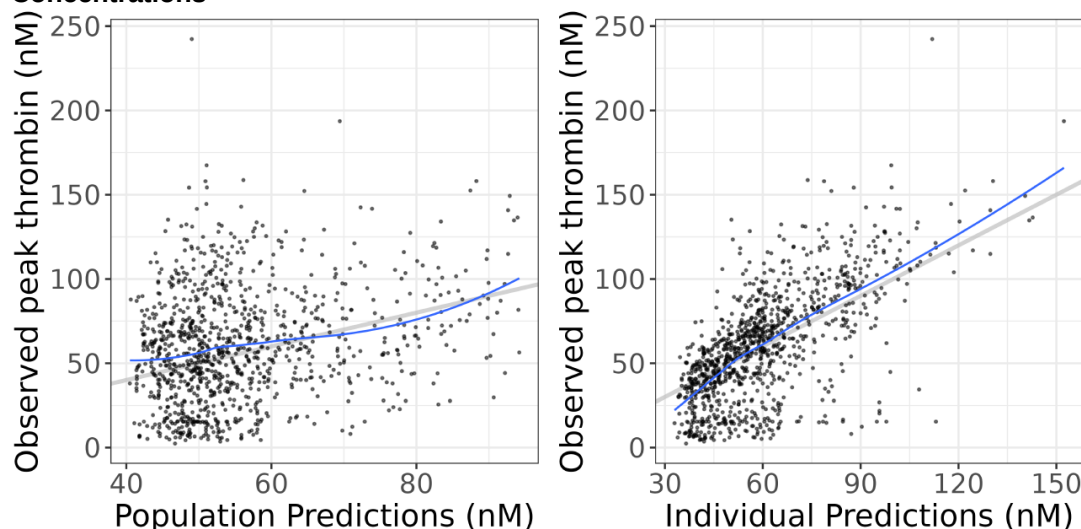


Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 24

The observed peak thrombin data is faceted by different studies in hemophilia patients. The blue line is population estimates obtained from the PKPD model and shows the overall relationship between model predicted free TFPI and observed peak thrombin values.

Abbreviations: PKPD, pharmacokinetics/pharmacodynamics; TFPI, tissue factor pathway inhibitor

[Figure 39](#) shows a comparison of the observed peak thrombin values with population predictions (left panel) and individual predictions (right panel) for the PKPD model, which displays a good agreement between observed values and the population/individual predictions from the model for peak thrombin values.

Figure 39. Goodness-of-Fit Plots With Population and Individual Predictions for Peak Thrombin Concentrations

Source: Population Modeling Analysis Report (PMAR Amendment) – Figure 21
 Line of unity is shown in gray. Loess fit of data is shown in blue.

The review team found the Applicant's PKPD model for free TFPI and thrombin peak acceptable with an adequate fit of the data as evident. In addition to the PKPD analyses, the review team explored conventional E-R analysis using PK exposure metrics (i.e., $C_{avg,ss}$) and the primary efficacy endpoint of ABR to better understand the appropriateness of the proposed dosing regimen of marstacimab.

14.5.2. Exposure-Response PK Analysis

The Applicant conducted the E-R analysis of efficacy using marstacimab PK and the primary efficacy endpoint, annualized bleed rate (ABR). The objective of the Applicant's E-R analysis was to support the dose justification for adult and adolescent participants with hemophilia.

Method

A Poisson regression analysis was used to describe the relationship between marstacimab exposure metrics (steady state C_{avg} , C_{max} and C_{min}) and number of bleeds for hemophilia participants. Doses evaluated were 150 mg SC QW (loading dose of 300 mg SC), 300 mg SC QW and 450 mg SC QW. The recommended clinical dose is 150 mg SC QW (loading dose of 300 mg SC), with a provision to escalate the dose to 300 mg SC QW. The marstacimab $C_{avg,ss}$ was calculated using post-hoc estimates obtained from the final PPK model. Age was explored in the model as a continuous covariate (not as separate age groups) and showed only a small effect on ABR.

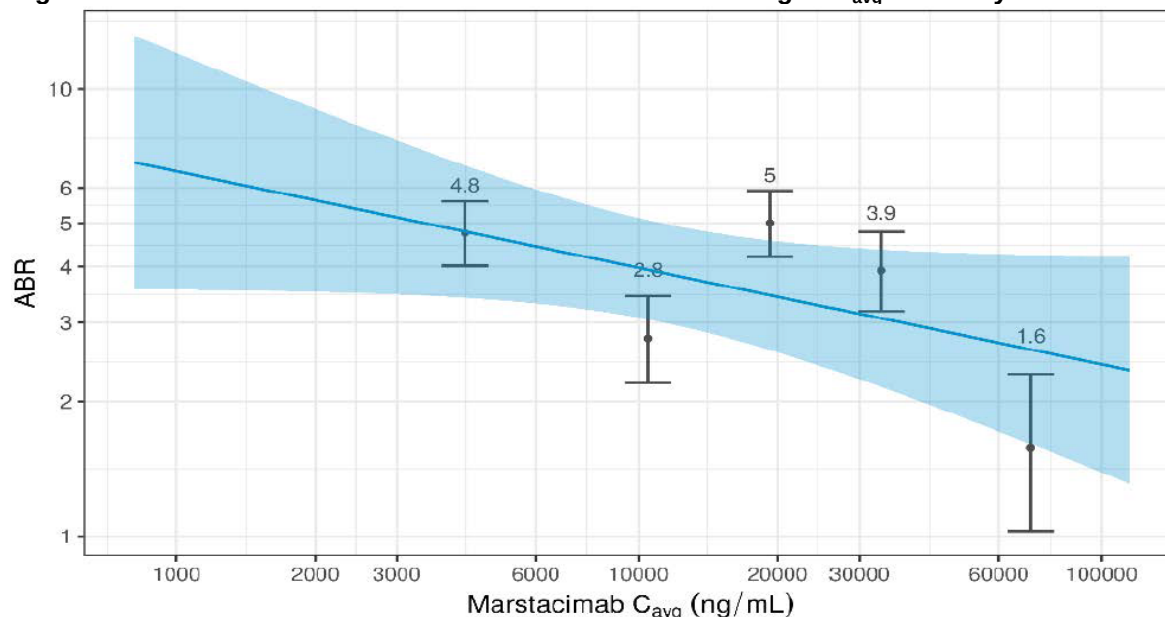
Results

The E-R analysis included number of bleeds for hemophilia patients in Phase 2 (Studies B7841002 and B7841003) and Phase 3 (Study B7841005) studies. The final model was a Quasi-Poisson regression model with log PK as the independent variable and ABR as the dependent

HYMPAVZI (marstacimab-hncq) injection

variable, which did not include any covariates. [Figure 40](#) shows the model fits of the final Quasi-Poisson model for marstacimab $C_{avg,ss}$ vs. ABR, which indicates a negative relationship between examined marstacimab exposure and ABR.

Figure 40. Model Fits for the Final E-R Model of ABR With Log of C_{avg} at Steady-State

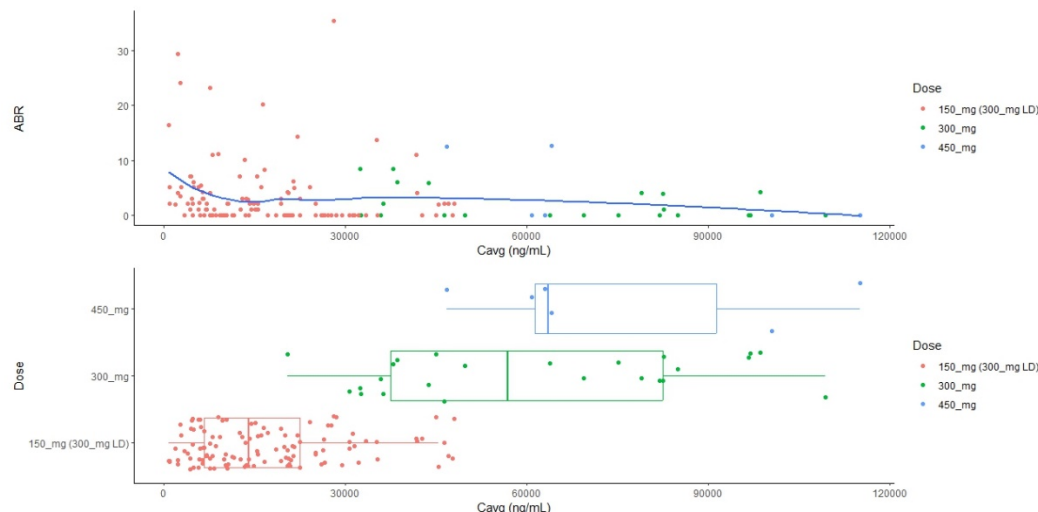


Source: Response to FDA Information Request-Received February 29, 2024 – Question 1, Figure 1

The x-axis shows steady state exposure metric in ng/mL of $C_{avg,ss}$. The y-axis shows ABR values (predicted from the Quasi-Poisson model or observed in the analysis population). The solid circles and error-bars (in black) show the observed mean ABR and 95% CI, respectively for each bin of exposure metric in the analysis population. The blue line, (and blue shaded area) are the model-predicted mean (and 95% CI) ABR for the range of observed exposure metric in the analysis population. The numbers above the error bars show the observed mean ABR values for each bin of exposure metric.

Abbreviations: ABR, annualized bleeding rates; C_{avg} , average plasma concentration; $C_{avg,ss}$, average plasma concentration at steady-state; CI, confidence interval; E-R, exposure-response

To evaluate whether the proposed dose is reasonable, E-R analysis was conducted with primary efficacy endpoint of ABR. The LOESS nonparametric regression method with data from the Phase 1b/2 study (Study B7841002), Phase 2 open-label extension study (Study B7841003), and Phase 3 study (Study B7841005) for doses 150, 300, and 450 mg was used in the E-R analysis. Fourteen participants who had dose escalated during the Phase 3 study were not included due to limited PK samples after dose escalation. [Figure 41](#) shows that there is a slight trend for decrease in ABR with increase in marstacimab exposure ($C_{avg,ss}$).

Figure 41. E-R Analysis for Primary Efficacy Endpoint of Annualized Bleeding Rate (ABR) With Three Marstacimab Administrations

Source: Reviewer's analysis

Loess fit is shown by the blue line in the top plot.

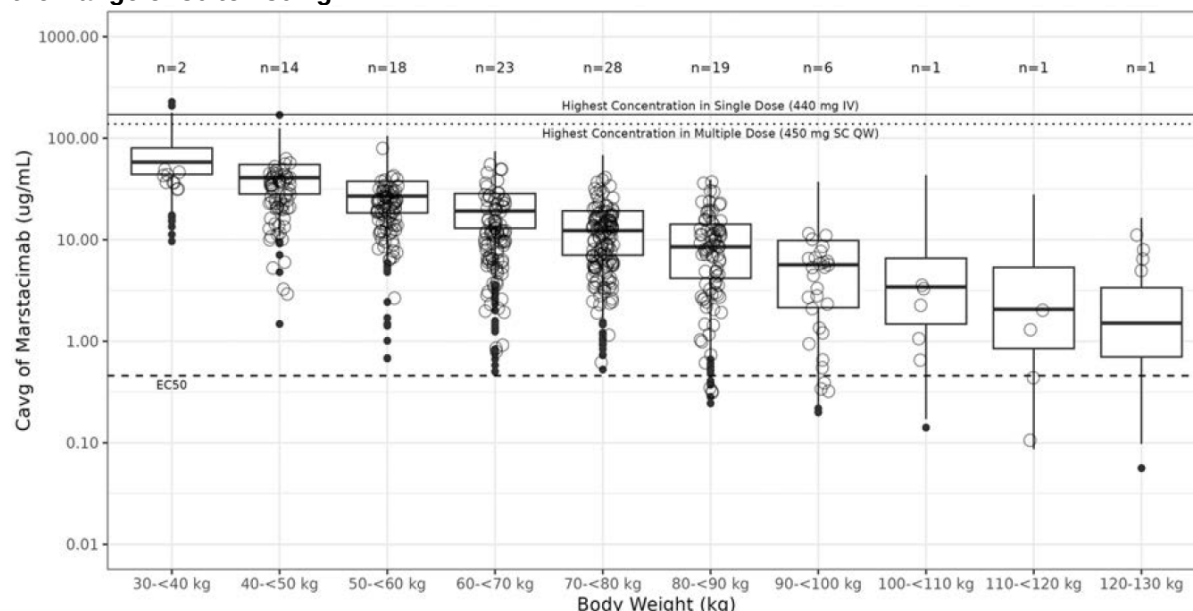
Abbreviations: C_{avg} , average plasma concentration; E-R, exposure-response; LD, loading dose

The review team found a similar trend as the Applicant's model, results of the E-R analysis show a trend for decreasing ABR with increasing concentrations, which is also consistent with the results from the previous PKPD analysis.

14.5.2.1. Phase 3 Dose Justification for Adolescents

The justification for same dose (150 mg SC once weekly, with 300 mg SC loading dose) for adolescents and adults in the Phase 3 study (Study B7841005) was based on the predictions from the previous PPK and PKPD model. To understand the weight effect on PK exposure metrics (steady state C_{avg} , C_{max} and C_{min}), the Applicant simulated a population with a uniform weight distribution in the range of 30 to 120 kg. 5000 participants were simulated in total, with approximately 500 participants in each weight category (every 10 kg increment). The pharmacokinetic exposure metrics were predicted from the final PPK model.

Box plots of simulated steady-state average for 150 mg SC QW across weight categories with observed data overlaid are shown in [Figure 42](#). PK simulations performed for weight categories based on observed weight distribution show that exposures (median $C_{avg,ss}$) were predicted to be around 4-fold higher for the 30 to 50 kg group and about 6-fold lower for the 100 to 130 kg group in comparison to predicted exposures for a reference (standard) weight group of 70 to 80 kg. In general, at lower weights, the higher concentrations were still below the maximum concentrations seen in clinical studies. At higher weights, concentrations were above the marstacimab plasma EC_{50} based on modeling of Phase 1 and 2 clinical data. In summary, an overlap was seen for the observed range of concentrations across the 40 to 50 kg to 80 to 90 kg weight categories.

Figure 42. Box Plots of Marstacimab $C_{avg,ss}$ (150 mg SC QW) for Weight Categories (Every 10 kg) in the Range of 30 to 130 kg

Source: Response to FDA Information Request-Received February 29, 2024 – Question 2, Figure 1

The plot shows simulated steady state marstacimab average concentration ($C_{avg,ss}$) grouped into different weight buckets of 10 kg with weights ranging from 30 kg to 130 kg. Closed circles show the outliers from simulated average marstacimab concentrations. Open circles show observed steady state average marstacimab concentrations. EC_{50} (marstacimab concentration in $\mu\text{g/mL}$) is based on modeling of animal and Phase 1/Phase 2 clinical data. The numbers above or below the bars show the number of participants in each weight category.

Abbreviations: $C_{avg,ss}$, average plasma concentration at steady state; EC_{50} , dose required for 50% of the population to obtain the therapeutic effect; n, number of participants in the subgroup; QW, once weekly; SC, subcutaneous

The review team found the Applicant's exposure response model to be acceptable. A slight trend for decreasing ABR with increasing concentrations was found by the E-R analyses. The 150 mg SC QW weekly with 300 mg SC loading dose is acceptable for most patients with a dose escalation that may benefit a small proportion of patients whose ABR is not adequately controlled. Overall, E-R and PKPD analyses support the proposed dosing regimen of marstacimab for the proposed indication, which is based upon the favorable safety and efficacy results of the studied clinical studies.

14.6. Pharmacogenetics

Not applicable.

15. Study / Trial Design

15.1. Clinical Protocol Synopsis, Study B7841005, Based on Amendment 7, March 24, 2022)

Table 98. Study Details, Study B7841005

Method	Details
Name of sponsor/company	Pfizer Inc.
Study number	B7841005
Study title	An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Hemophilia A Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis
Name of study intervention	PF-06741086 (marstacimab)
Investigational sites	This is an international, multicenter study to be conducted at approximately 52 Sites.
Phase	3

Source: FDA table based on Clinical Protocol

Rationale

Treatment with marstacimab is anticipated to demonstrate a clinically relevant advantage or a major contribution to patient care in comparison to current methods of treatment for hemophilia A or B because it works differently than factor replacement products and its anticipated efficacy is not expected to be impacted by the presence of inhibitors. The potential for once weekly (QW) subcutaneous (SC) administration provides for treatment options in the absence of reliable vascular access, increased convenience and may enable better compliance. Combined, these qualities should result in a reduction of bleeding episodes.

Objectives

Primary Objectives

- To demonstrate the efficacy and safety of marstacimab for routine prophylaxis 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

Secondary Objectives

- To evaluate additional efficacy of marstacimab
- To evaluate the effect of marstacimab on Health-related quality of life (HRQoL)

Tertiary/Exploratory Objectives

- Assess PK and PD parameters in this study population
- To evaluate the effect of marstacimab on Health-related quality of life
- To compare joint health post marstacimab to baseline
- To evaluate the effect of marstacimab on total coagulation factor or bypass product consumption

Overall Design

This is a one-way, cross-over, open-label, multi-center study in approximately 145 adolescent and adult participants between ages 12 to <75 years with severe hemophilia A or moderately severe to severe hemophilia B (defined as FVIII activity <1% or FIX activity $\leq 2\%$, respectively) with or without inhibitor, with approximately 20% of participants as adolescents (ages between 12 to <18 years old). Additional participants (approximately 20%) may be recruited for this study in order to account for attrition of enrolled participants and to provide for sufficient representation into regions which have experienced recruitment delays due to the COVID-19 pandemic. This study is comparing treatment with their prescribed factor replacement therapy or bypass therapy during an observational phase with a 12-month Active Treatment Phase, during which participants will receive prophylaxis (defined as treatment by SC injection of marstacimab [PF-06741086]).

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

Disclosure Statement

This is a Cross-Over Prevention study with one arm which has no masking

Number of Participants

- Approximately 145 participants (approximately 20% adolescents) will be enrolled:
- Approximately 45 participants (approximately 35 hemophilia A and 10 hemophilia B participants) in the Inhibitor Cohort;
- Approximately 100 participants (approximately 80 hemophilia A and 20 hemophilia B participants) in the Non-Inhibitor Cohort.
- The Inhibitor Cohort (n=45) will include at least 5 adolescent participants and the Non-Inhibitor Cohort will include at least 20 adolescent participants.

Intervention Groups and Duration

Enrollment of individuals into the Observational Phase who are on prior on-demand or prophylaxis treatment will begin at the same time.

Prior On-Demand Treatment

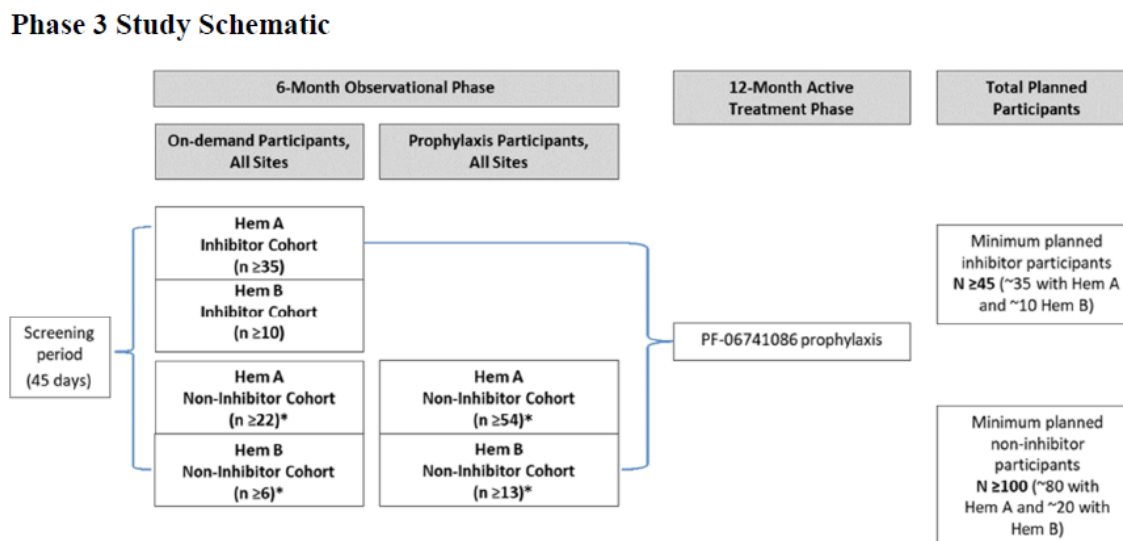
Participants with either hemophilia A or B, with or without inhibitors, and who are prescribed an on-demand treatment regimen during the observational phase will transition to the Active Treatment Phase after approximately 6 months. Individuals with inhibitors will receive on-demand treatment with recombinant factor VIIa (rFVIIa), Prothrombin Complex Concentrates (PCC), or activated Prothrombin Complex Concentrates (aPCC) agents e.g., FEIBA or in regions where available, BYCLOT (Inhibitor Cohort) and individuals without inhibitors will receive on on-demand treatment with FVIII- or FIX-replacement therapy (noninhibitor cohort) during the observational phase before crossing over to the 12-month active treatment phase.

Prior Prophylaxis Treatment

Participants without inhibitors who were on prior prophylactic treatment with FVIII- or FIX-replacement (defined as treatment by intravenous injection of factor concentrate to prevent bleeding) during the observational phase will transition to the Active Treatment Phase after approximately 6 months.

Study Duration

The anticipated study duration for an individual participant is approximately 21 months, including an approximately 45-day Screening period, an observational phase of approximately 6 months, a 12-month active treatment phase during which the participant receives an initial loading dose followed by prophylaxis treatment with PF-06741086, and a 1-month follow-up for safety monitoring.

Figure 43. Phase 3 Study Schematic

*Remaining 5 participants will be allocated to the non-inhibitor cohorts at the discretion of the sponsor.

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

Source: Study B7841005 Protocol schema

Abbreviations: FIX, factor IX; FVIII, factor VIII; Hem A, hemophilia A; Hem B, hemophilia B; N, overall number of participants; n, number of participants in subgroup

Study Population

Inclusion Criteria

1. Male age 12 to <75 years inclusive with a minimum body weight of 35 kg.
2. Participants with a diagnosis of severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) documented by clinical laboratory prior to enrollment. The severity of hemophilia 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.
3. Participants who are enrolled into the non-inhibitor cohort must also meet the following criteria:

HYMPAVZI (marstacimab-hncq) injection

- 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).
- Subjects receiving routine prophylaxis 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

- Subject with on-demand treatment regimen with ≥ 6 acute bleeding episodes (spontaneous and/or traumatic) that required coagulation factor infusion during the 6 months period prior to screening and willing to continue to receive on-demand treatment during the observational phase. Surgical bleeding episodes do not apply to this criterion.

Exclusion Criteria

1. Previous or current treatment for or history of coronary artery diseases, venous or arterial thrombosis (Common Terminology Criteria for Adverse Events [CTCAE] Grade >1), or ischemic disease (except for catheter-associated thrombosis).
2. Known planned surgical procedure during the planned study period.
3. Known hemostatic defect other than hemophilia A or B.
4. Abnormal renal or hepatic function as defined by the following laboratory results at screening:
 - a. Alanine transaminase (ALT) $>2 \times$ ULN.
 - b. Bilirubin $>1.5 \times$ ULN (isolated bilirubin $>1.5 \times$ ULN is acceptable if bilirubin is fractionated and direct bilirubin $<35\%$).
 - c. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal 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.
 - a. Serum albumin less than the lower limit of normal (LLN).
 - b. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m².
5. Abnormal hematology values as defined by the following laboratory tests at Screening:
 - a. Platelet count $<100,000/\mu\text{L}$
 - b. Hemoglobin level <10 g/dL
6. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.

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7. QTcF >450 msec or QTcF >480 msec in subjects with bundle branch block.
8. Participants with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.
9. Current routine prophylaxis with bypassing agent (e.g., aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), noncoagulation nonfactor replacement therapy (e.g., emicizumab), or any previous treatment with a gene therapy product for treatment of hemophilia.
 - 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 nonfactor-based hemophilia therapy (e.g., fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.
10. Regular, concomitant therapy with immunomodulatory drugs (e.g., IV immunoglobulin [IVIG], and routine systemic corticosteroids, rituximab).
11. Ongoing or planned use of immune tolerance induction during the OP or ATP, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the ATP.
12. 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.
13. Previous exposure to marstacimab during to participation in Studies B7841002 and B7841003.
14. CD4 cell count $\leq 200/\mu\text{L}$ if human immunodeficiency virus (HIV)-positive.
15. Screening 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

Treatment of Breakthrough Bleeding

During OP: Patients experience acute bleeding episode should be stabilized utilizing the patient's standard hemostatic treatment regimen, which may include FVIII- or FIX replacement therapy.

During the ATP: Patients experience breakthrough bleeding judge by the investigator or treating physician to require additional hemostatic therapy beyond PF-06741086 prophylaxis, FVIII- or FIX- or FIX-replacement products may be administered at the lowest effective dose and according to the approved product labeling.

Prohibited Medications

Immunomodulatory medications (e.g., IVIG, routine systemic corticosteroids, rituximab), emicizumab, bypassing agent (rFVIIa, PCC, aPCC, or BYCLOT) were prohibited throughout all phases of the study.

Systemic antifibrinolytic agents or medications known to influence platelet function (e.g., aspirin or certain non-steroidal anti-inflammatory drugs) require a washout of ≥ 120 hours prior to

administration of study intervention on Day 0 through completion of ATP Day 360 (Visit 20) in the Active Treatment Phase.

Study Intervention Compliance

Participant compliance with completion of eDiary and study intervention injections will be assessed at each visit. Compliance will be assessed by review of the eDiary. Participants must maintain at least 80% compliance with weekly dosing of PF-06741086.

Dose Modification

The dose may be escalated after 6 months of active treatment with marstacimab, and at any time after completion of Visit 14 (ATP Day 180), from 150 mg SC QW to 300 mg SC QW if the following criterion is met:

- Weigh at least 50 kg and not adolescent.
- 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.

Schedule of Visit**Table 99. Schedule of Activities (SoA)**

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
Informed consent	X				When required by local regulation, participants <18 years of age will complete an additional informed consent (specifically, the Minor Assent Form). Minor participants must be reconsented if they reach the age of majority during the course of the study, in order to continue participating.
Confirm inclusion and exclusion criteria are met	X	X			
Medical history	X				Includes hemophilia history and inhibitor history, and the number of bleeding episodes over the past 6 months. Any significant medical history for the life of the participant should be reported.
Demography	X				
Height and Weight	X				
Full Physical examination	X				
Brief physical examination		X			Brief examination based on signs and symptoms of the participant and will assess changes from baseline or previous physical examination of any ongoing signs or symptoms.
Vital signs	X	X			Obtain pulse rate, respiratory rate, temperature, and blood pressure (after participant has been in a seated or supine position for at least 5 minutes).

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Hemophilia Joint Health Score (HJHS)		X			Details related to performing the HJHS can be found in Section 8.1.6 .
Laboratory					FVIII or FIX activity can be analyzed either at a local clinical laboratory or at the central laboratory. Cardiac troponin (cTnI) assessments, where available (only at sites where the local laboratory will provide these results) will be analyzed by the local and central laboratories. All other laboratory tests will be analyzed at the central laboratory. Refer to Section 10.2 for details.
FVIII or FIX Inhibitor	X				Central laboratory analysis of FVIII or FIX Inhibitor will be performed using the Nijmegen modification of the Bethesda Inhibitor Assay. The central laboratory result will be used to make the final determination for each cohort assignment. However, until the central lab results are available, local laboratory results of FVIII or FIX inhibitor concentrations may be used to determine eligibility for enrollment.

HYMPAVZI (marstacimab-hncq) injection

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
FVIII or FIX activity		X			If documented historic qualifying FVIII or FIX activity is not available then FVIII or FIX Activity bioanalysis will be analyzed by a clinical laboratory (either a local laboratory or the central laboratory used in this study). If FVIII or FIX activity samples need to be obtained during Screening to document activity then the following steps need to be taken: • Samples collected for the Baseline (Visit 2) visit should be obtained during the period between Visit 1 and Visit 2 allowing sufficient time for a minimum washout period completed for the prescribed factor-replacement product. • For individuals who are on extended half-life products the minimum washout can be adjusted to reflect individual PK values based on the participant's historical values, when available, and if appropriate in the medical judgement of the investigator (eg, the washout period may be adjusted to 4 times of an individual's half-life). • If a participant experiences an acute bleeding episode during this washout period requiring treatment with a FVIII or FIX replacement therapy, or bypass agent therapy, the participant is to be stabilized utilizing this regimen and a new washout period should be initiated (Section 6.5.1).

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
Informed consent	X				When required by local regulation, participants <18 years of age will complete an additional informed consent (specifically, the Minor Assent Form). Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
Confirm inclusion and exclusion criteria are met	X	X			
Medical history	X				Includes hemophilia history and inhibitor history, and the number of bleeding episodes over the past 6 months. Any significant medical history for the life of the participant should be reported.
Demography	X				
Height and Weight	X				
Full Physical examination	X				
Brief physical examination		X			Brief examination based on signs and symptoms of the participant and will assess changes from baseline or previous physical examination of any ongoing signs or symptoms.
Vital signs	X	X			Obtain pulse rate, respiratory rate, temperature, and blood pressure (after participant has been in a seated or supine position for at least 5 minutes).

HYMPAVZI (marstacimab-hncq) injection

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
PT/INR		X	→	→	The Day 0 Pre-Dose results (during Active Treatment Phase) are required prior to dosing, in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0. Results can be obtained at any time from the Enrollment (Visit 2) visit through the Day 0 Pre-Dose (Visit 7 Pre-Dose) visit.
Biomarker (Fibrinogen)		X	→	→	The Day 0 Pre-Dose results (during Active Treatment Phase) are required prior to dosing, in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0. Results can be obtained at any time from the Enrollment (Visit 2) visit through the Day 0 Pre-Dose (Visit 7 Pre-Dose) visit.
Hematology and Serum Chemistry	X				Collect following at least a 12-hour fasting period.
Serology Tests	X				Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, HIV (including CD4 count).
Cardiac troponin I (cTnI)	X				Only sites with the cTnI assay available at their local laboratory will collect cTnI samples for central and local analysis. If cTnI results are abnormal, the investigator should first consult with a cardiologist concerning cTnI and electrocardiogram (ECG) results, and outcome of cardiac consult is then discussed with the Pfizer medical monitor to determine appropriate course of action. When possible, the participant should return within 24 hours for repeated cTnI sample collection.

HYMPAVZI (marstacimab-hncq) injection

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
ECG	X				Triplicate ECGs will be obtained, approximately 2-4 minutes apart, at the same time as collection of all cTnI samples when the participant is in a supine position, including scheduled sample collection and any follow-up sample collection performed during study participation. The average of the triplicate ECG measurements collected at each nominal time point during Observational Phase Visit 1 will serve as each participant's baseline value (see Appendix 9 for examples of abnormalities). At sites where cTnI results are available and when abnormal, triplicate ECGs should be obtained if the participant is available to return for optional repeated cTnI sample collection within 24 hours. Interpretation for all abnormal ECGs and any ECGs obtained at the time of an abnormal cTnI laboratory value will be provided by central reader at the core ECG laboratory.
Cohort Assigned		X			Participants are assigned to appropriate cohort, including "Hemophilia A or B", "Inhibitor or Non-Inhibitor", "Prophylaxis or On-Demand", "Adult or Adolescent".
Currently Prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT	→	→	→	→	Review use of FVIII or FIX replacement therapy, or bypass agent therapy for any changes since the previous visit. Use of these medications will be recorded in the participant's diary.
Discontinue prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT				X	Discontinue scheduled use of FVIII, FIX, rFVIIa, aPCC, PCC, or BYCLOT prior to initiating study intervention in ATP Day 0. Prescribed FVIII, FIX, rFVIIa, aPCC, or BYCLOT may still be used as described in Section 6.5.1 .

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
eDiary Entries		→	→	→	Bleed, non-study intervention infusion, and study intervention injection entries, as applicable. Refer to Study Reference Manual for complete instructions on eDiary entries and reporting injection site reactions.
eDiary Dispensed and Training		X			At Baseline, an electronic handheld device will be dispensed to each participant to enable completion of the bleed and infusion (logs) diary. Participants will be provided training with respect to completing the diary (including timing and nature of information to be entered). At all visits after Enrollment, the participant diary is reviewed to ensure compliance with prescribed hemophilia treatments (including those used to treat breakthrough bleeding), and assessment of bleeds (including bleeding site and if bleeds are "spontaneous" or "traumatic"). Any non-compliance will be documented and participant will be provided additional training, as required. Note: until eDiary is available, a paper diary may be used throughout the study.
eDiary Data Reviewed		X	X	X	

HYMPAVZI (marstacimab-hncq) injection

	Observational Phase (OP)				Notes
Visit Identifier	Visit 1 Screening	Visit 2 Baseline	Visits 3-4 Interim Phone Call	Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. A face to face clinic visit may replace the Interim Phone Call and Phone Follow-Up visits if they overlap with the participant's usual care visit or at the discretion of the investigator. It is recommended that OP Phone Follow-Up (Visit 5) visit should occur at the same time as Active Treatment Phase Day -7 (Visit 6). If Visit 5 and Visit 6 are not completed on the same day, Visit 6 Day -7 must be completed the next calendar day after Visit 5.
	OP Day -45 to -1	OP Day 1 Enrollment	Every 60 days	180 (±14) days from Day 1	
Visit Window	-----	-----	±7 days	-----	
Patient Reported Outcomes (Questionnaires) Completion on site tablet		X			Participants will complete health outcome-related questionnaires using an electronic tablet device provided by the site at these visit dates, within the allowed visit windows. These health outcome-related questionnaires must be completed prior to any other scheduled study procedures at each visit/timepoint. In order to avoid introduction of any bias, study staff are not permitted to have discussions related to the participant's quality of life, ie, "How are you feeling?" prior to completion of the questionnaires. Study staff members are permitted to assist participants with any technical difficulties related to the use of the electronic device. The Patient's Global Impression of Change – Hemophilia (PGIC-H) will not be administered at this visit.
Prior and concomitant Treatment(s)	X	→	→	→	Includes prior and concomitant medication and non-medication treatments, such as surgeries and procedures within the 1 year prior to obtaining informed consent.
Serious and non-serious adverse event monitoring	X	→	→	→	

		Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator.	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call	When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments.
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>
Vital Signs		X	X		X	X		X		X		X		X		X		Obtain pulse rate, respiratory rate, temperature, and blood pressure (after participant has been in seated or supine position for at least 5 minutes).
Full Physical Examination		X														X		
Brief Physical Examination					X	X				X				X				Limited examination based on signs and symptoms of the participant and will assess changes from baseline or previous physical examination of any ongoing signs or symptoms.
Hemophilia Joint Health Score (HJHS)		X				X				X		X		X		X		Details related to performing the HJHS can be found in Section 8.1.6 .
Height and Weight		X								X				X		X		

HYMPAVZI (marstacimab-hncq) injection

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
Investigational Medication Accountability					X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Medication Return					X	X		X		X		X		X		X	
Medication Error			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
Laboratory																	FVIII or FIX activity can be analyzed either at a local clinical laboratory or at the central laboratory. Cardiac troponin (cTnI) assessments, where available (only at sites where the local laboratory will provide these results) will be analyzed by the local and central laboratories. All other laboratory tests will be analyzed at the central laboratory.
FVIII or FIX Inhibitor	X								X						X*		FVIII or FIX Inhibitor bioanalysis will be analyzed by the central laboratory. The central laboratory result will be used to make the final determination for each cohort assignment. However, until the central lab results are available, sites may use a local lab result to progress the participants in the study. *This sample is collected from all adult participants; however, only collect this sample from adolescent participants if their weight is >40 kg at Visit 20.

HYMPAVZI (marstacimab-hncq) injection

		Active Treatment Phase (ATP)															Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>
FVIII or FIX activity		X							X						X*		FVIII or FIX Activity bioanalysis will be analyzed by a local laboratory OR the central laboratory. FVIII or FIX activity: Samples collected at the Visit 7 (ATP Pre-Dose) must be after minimum washout period completed for prescribed factor-replacement product. For individuals who are on extended half-life products the minimum washout can be adjusted to reflect individual PK values based on the participants historical values, when available, and if appropriate in the medical judgement of the investigator (eg, the washout period may be adjusted to 4 times of an individual's half-life). If a participant experiences an acute bleeding episode during this washout period requiring treatment with FVIII or FIX replacement therapy, or bypass agent therapy, the

	Active Treatment Phase (ATP)															Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
																participant is to be stabilized utilizing this regimen and a new washout period should be initiated (Section 6.5.1). *This sample is collected from all adult participants; however, only collect this sample from adolescent participants if their weight is >40 kg at Visit 20.
Hematology and Serum Chemistry (with lipid profile)	X				X				X				X*		X	
Urinalysis		X			X				X				X		X	

		Active Treatment Phase (ATP)																Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments.		
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>		
PT/INR	→	X	X	X		X				X			X		X		The Day 0 Pre-Dose results are required prior to dosing, in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0. Results can be obtained at any time from the Enrollment (Visit 2) visit through the Day 0 Pre-Dose (Visit 7 Pre-Dose) visit.		
aPTT		X	X	X		X				X			X		X				
Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level			→	→	→	→	→	→	→	→	→	→	→	→	→		Samples are only collected and analyzed if a participant experiences a thrombotic event at any time during the Active Treatment Phase. If the site becomes aware of the occurrence of a thrombotic event, the investigator (or designee) should collect these samples at the earliest opportunity for analysis at the central laboratory. All samples collected will be analyzed.		

		Active Treatment Phase (ATP)															Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u> Anti-drug antibodies and neutralizing antibodies to PF-06741086. Hepatitis B surface antigen, hepatitis B core antigen antibody, hepatitis C virus antibody, HIV (and CD4 count).
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
Immunogenicity Tests	X				X	X		X				X		X		X	
Serology Tests	X																

HYMPAVZI (marstacimab-hncq) injection

	Active Treatment Phase (ATP)																Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call	
Visit Window (days)	=10			=2	=7	=7	=7	=7	=7	=7	=7	=7	=7	=7	=2	=2	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>	
PF-06741086 concentration		X		X	X	X		X				X		X		X**	PF-06741086 concentration, record date and time of previously administered dose and actual date and time of sample collection. For participants who come to the study center for dose administration on Days 7, 28, or 60, it is recommended that PK sample be obtained before dose administration occurs. Dosing should not be delayed or withheld in the event that the PK blood sample cannot be taken before dose administration. Any participant who discontinues study participation prior to the Active Treatment Phase are not required to provide a PF-06741086 sample for analysis at the ATP Day 360 / Study Completion/Termination Visit (Visit 20). **These samples are collected from all adult participants; however, do not collect this sample from any adolescent participants at Visit 20.	

	Active Treatment Phase (ATP)																Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	
Biomarkers (TFPI, PF1+2, D-dimer, dPT, TGA)		X		X	X		X		X*		X		X		X**			Tissue factor pathway inhibitor (both Total TFPI and Free TFPI), PF1+2, D-dimer, dilute prothrombin time, thrombin generation assay. "Free" TFPI will only be analyzed if this assay is validated before the study completes. No additional sample volume is required for this test. *At this timepoint (Visit 14), ONLY collect samples for analysis of PF1+2 and D-dimer. DO NOT collect samples to analyze TFPI, dPT, and TGA. **These samples are collected from all adult participants; however, dilute prothrombin time (dPT) will not be collected from any adolescent participants at Visit 20.

HYMPAVZI (marstacimab-hncq) injection

		Active Treatment Phase (ATP)																Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>		
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit		ATP Day 390 Follow-up Phone Call	
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2		±2	
Biomarker (Fibrinogen)	→	X		X		X		X		X		X		X		X			

		Active Treatment Phase (ATP)																			Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u> Only sites with the cTnI assay available at their local laboratory will collect cTnI samples for central and local analysis. cTnI samples will be collected during the Active Treatment Phase at Visit 7 (ATP Day 0 Pre-Dose), Visit 14 (ATP Day 180 Visit), and Visit 20 (Study Completion/Termination Visit). If cTnI results are abnormal, the investigator should first consult with a cardiologist concerning cTnI and electrocardiogram (ECG) results, and outcome of the cardiac consult is then discussed with the Pfizer medical monitor to determine appropriate course of action. When possible, the participant should return within 24 hours for repeated cTnI sample collection.				
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit		ATP Day 390 Follow-up Phone Call			
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2		±2			
Cardiac troponin I (cTnI)		X								X						X					
ECG		X								X						X					

HYMPAVZI (marstacimab-hncq) injection

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
																	including scheduled sample collection and any follow-up sample collection performed during study participation (see Appendix 9 for examples of abnormalities). At sites where cTnI results are available and when abnormal, triplicate ECGs should be obtained if the participant is available to return for optional repeated cTnI sample collection within 24 hours. Interpretation for all abnormal ECGs and any ECGs obtained at the time of an abnormal cTnI laboratory value will be provided by central reader at the core ECG laboratory.
Study intervention administered at study center and as needed			X	X	X	X											On Visit 7 (ATP Post-dose), study intervention will be administered by the site staff and recorded in the CRF. All other doses will be administered by the participant/caregiver and documented in the eDiary. Participant or caregiver will be retrained on study intervention administration, if required. For participants who come to the study center for dose

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
																	administration on Days 7, 28, or 60, it is recommended that PK sample be obtained before dose administration occurs. Dosing should not be delayed or withheld in the event that the PK blood sample cannot be taken before dose administration. Study intervention will be administered once weekly (QW). See Section 6.4 for details if participant misses a scheduled dose. Participants not continuing into the long-term extension study or not continuing treatment with study intervention will be eligible to resume treatment with their regularly prescribed hemostatic product (see Section 6.5.1). However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).

HYMPAVZI (marstacimab-hncq) injection

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>
Study intervention administered by participant/caregiver				X	X	X	X	X	X	X	X	X	X	X	X		Doses administered by the participant/caregiver may be administered by the study center, as needed. Study intervention will be administered once weekly (QW). See Section 6.4 for details if participant misses a scheduled dose. Participants not continuing into the long-term extension study or not continuing treatment with study intervention will be eligible to resume treatment with their regularly prescribed hemostatic product (see Section 6.5.1). However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).
Dispense Investigational Medication				X	X	X		X		X		X		X			Dispense sufficient quantity of study intervention until the next scheduled in-person visit

	Active Treatment Phase (ATP)																Notes
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2	Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u>
Currently prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT for on-demand treatment only	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Use of these medications are collected in the eDiary.
eDiary Entries			→	→	→	→	→	→	→	→	→	→	→	→	→		eDiary Entries: Bleed, non-study intervention infusions, and study intervention injections entries, as applicable.
eDiary Data Reviewed				X	X	X	X	X	X	X	X	X	X	X	X		

HYMPAVZI (marstacimab-hncq) injection

	Active Treatment Phase (ATP)															Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
eDiary Collected																X	Note: until eDiary is available, a paper diary may be used throughout the study. eDiary Data Reviewed: Participant diary is reviewed, including compliance with study intervention treatment (PF-06741086) and medications prescribed for breakthrough bleeding, and assessment of bleeds (including bleeding site and if bleeds are “spontaneous” or “traumatic”). Any non-compliance will be documented and participant will be provided additional training, as required.

	Active Treatment Phase (ATP)															Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit	ATP Day 390 Follow-up Phone Call
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2	±2
Patient Report Outcomes (Questionnaires) Completion on site tablet	X	X				X		X		X		X				X	Participants will complete health outcome-related questionnaires using an electronic tablet device provided by the site at these visit dates, within the allowed visit windows. These health outcome-related questionnaires must be completed prior to any other scheduled study procedures at each visit/timepoint. In order to avoid introduction of any bias, study staff are not permitted to have discussions related to the participant's quality of life, ie, “How are you feeling?” prior to completion of the questionnaires. Study staff members are permitted to assist participants with any technical difficulties related to the use of the electronic device. Administration of the 2 Patient Global Impression of Change – Hemophilia (PGIC-H) versions will be as follows: PGIC-H (Observational Phase) completed by participants at Visit 6; PGIC-H (Active Treatment Phase) completed by participants at Visits 10, 12, 14, 16, and 20.

		Active Treatment Phase (ATP)																Notes	
Visit	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	A face-to-face visit may be conducted instead of a phone call if the scheduled study visit will occur at the same time as a participant's usual care visit or at the discretion of the investigator. When conducting an in-person or telephone visit with the participant, remind them of the next scheduled study visit. During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments. Participants who will participate in the planned B7841007 long-term extension study will continue to receive study intervention without interruption as they transition from B7841005 to B7841007. These participants are not required to complete the ATP Day 390 Follow-up Phone Call. <u>For participants who do not enroll into the planned B7841007 study, they may resume individual pre-study factor-based and bypassing treatment regimens immediately after discontinuing PF-06741086. However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).</u> Investigator will determine if dose-escalation criteria have been met, following 6 months of treatment with study intervention. If dose-escalation criteria met, participant's dose of PF-06741086 may increase from 150 mg once weekly to 300 mg once weekly. Includes concomitant medication and non-medication treatments such as surgeries and procedures.		
Visit Identifier	ATP Day -7 Visit	ATP Day 0 Pre-Dose	ATP Day 0 Post-Dose	ATP Day 7 Visit	ATP Day 28 Visit	ATP Day 60 Visit	ATP Day 90 Phone Call	ATP Day 120 Visit	ATP Day 150 Phone Call	ATP Day 180 Visit	ATP Day 210 Phone Call	ATP Day 240 Visit	ATP Day 270 Phone Call	ATP Day 300 Visit	ATP Day 330 Phone Call	ATP Day 360 Study Completion/ Termination Visit		ATP Day 390 Follow-up Phone Call	
Visit Window (days)	±10			±2	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±2		±2	
Dose Escalation Assessment										X	→	→	→	→	→	X			
Concomitant Treatment(s)			X	→	→	→	→	→	→	→	→	→	→	→	→	→		→	
Serious and non-serious adverse event monitoring	X	→		→	→	→	→	→	→	→	→	→	→	→	→	→	→		

Source: Study B7841005 Clinical Protocol

16. Efficacy

16.1. Derivation of the Noninferiority Margins for Major Efficacy Endpoints for Routine Prophylaxis

The section described the Applicant's derivation of the noninferiority (NI) margins for the bleeding-related primary and key secondary endpoints for routine prophylaxis.

Noninferiority Margin for the Primary Endpoint (ABR for Treated Bleeds)

In the statistical analysis plan (SAP) v6 dated January 31, 2023, the Applicant stated that historical data were selected from among the Applicant's hemophilia studies. This enabled selection of individual participant level data that would closely match the inclusion/exclusion criteria of Study B7841005. In selecting studies, the following aspects were considered: (1) having both prophylaxis and on-demand treatment, providing a within-study treatment difference estimate, (2) having an overlapping age group of 12 to 74 years old to match Study B7841005

HYMPAVZI (marstacimab-hncq) injection

age group, and (3) not being a regional study. The following three studies satisfied these criteria: B1821010 (BeneFIX), B1821002 (BeneFIX), and B1831004 (Xyntha/ReFacto).

- B1821010 was an open-label 1-way crossover study comparing the efficacy and safety between on-demand treatment and prophylactic therapy using BeneFIX in hemophilia B participants age 12 to 65 years old and factor IX activity level 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 international units [IU]/kg once-weekly dose, 12 months).
- B1821002 was an open-label, randomized, 4-period crossover study in males with hemophilia B, age 6 to 65 years old with factor IX activity level not greater than 2% intended to compare on-demand administration and two prophylaxis regimens. The study was comprised the following four 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 (randomized), 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 the safety and efficacy of ReFacto AF in hemophilia A participants switching to ReFacto AF from ReFacto or other factor VIII products in usual care settings. The participants were age 12 and greater and had factor XIII activity level <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.

[Table 100](#) presents the Applicant's analyses of the ABR of treated bleeds based on participant-level data from three hemophilia studies with inclusion/exclusion criteria that closely matched those for Study B7841005. The mean ABR difference between prophylaxis and on-demand treatment was estimated using three analyses: t-test allowing for nonhomogeneous variances, Hodges-Lehman location-shift parameter estimation, and additive negative binomial model. All analyses resulted in similar estimated mean differences of approximately 21, and the lower bound of 2-sided 95% confidence intervals ranging from 16.8 to 17.6.

During the review, the review team sent an IR and requested the Applicant to (1) clarify if the three studies [i.e., B1821010 (BeneFIX), B1821002 (BeneFIX), and B1831004 (Xyntha/ReFacto)] were based on hemophilia A or B participants with and without inhibitors, or based only on participants without inhibitors; and (2) provide the potential NI margins for all major efficacy endpoints based only on participants without inhibitors. The Applicant responded that the three internal studies included only enrolled participants without inhibitors.

Table 100. Analyses of Bleeding in Three Hemophilia Studies Used in Deriving the Noninferiority Margin

Parameter	BeneFIX B1821010	BeneFIX B1821002	Xyntha/ReFacto AF B1831004	Overall
On demand				
N	22	9	52	83
Mean ABR (95% CI) ¹	31.5 (24.3, 40.7)	26.3 (16.9, 41.0)	28.5 (22.7, 35.7)	29.0 (24.6, 34.3)
Prophylaxis				
N	22	9	154	185
Mean ABR (95% CI) ¹	4.0 (2.2, 7.2)	2.6 (0.8, 8.4)	7.9 (6.2, 10.2)	7.2 (5.7, 9.0)
ABR Ratio (95% CI) ² : Prophylaxis/on – demand	0.13 (0.08, 0.19)	0.10 (0.03, 0.29)	0.28 (0.18, 0.42)	0.25 (0.18, 0.34)
ABR difference (95% CI): On demand – prophylaxis				
D1: t-test Satterthwaite	27.4 (20.6, 34.3)	23.7 (11.5, 36.0)	19.9 (14.0, 25.8)	21.3 (16.8, 25.9)
D2: Hodges Lehman	26.8 (20.3, 34.3)	24.4 (10.2, 39.6)	19.5 (16.0, 23.5)	20.8 (17.3, 24.8)
D3: additive NB	27.5 (21.1, 33.8)	23.7 (13.8, 33.6)	20.5 (10.3, 30.8)	21.9 (17.6, 26.2)

Source: Study B7841005 SAP v6 dated January 31, 2023, Appendix Table A4.1.1.1

¹ Model-based from negative binomial regression

² Negative binomial regression

D1: t-test for unequal variances assuming independence

D2: HL location shift parameter estimate assuming independence except for BeneFIX studies

D3: additive negative binomial model using identity link.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; NB, negative binomial

Based on the lower bound of the confidence interval of this estimate, the ABR was assumed to be higher in patients receiving on-demand compared to prophylaxis by at least 16.8, which was considered margin 1 (M_1) in the noninferiority test setting.

Given the large effect size of prophylaxis treatment, an appropriate value for margin 2 (M_2) was considered in order to preserve a sufficiently large proportion of this effect. A value of 2.5 for M_2 (~85% effect preserved) was selected as both clinically meaningful and yielding a reasonable sample size.

Noninferiority Margin for Key Secondary Endpoint (ABR for Joint Bleeds)

The Applicant conducted analyses based on the two BeneFIX studies since the ReFacto study did not utilize this endpoint. All analyses resulted in similar estimated mean ABR differences of approximately 21 with the lower bound of 2-sided 95% confidence intervals ranging from 15.2 to 16.5. Therefore, the on-demand ABR was assumed to be higher than the prophylaxis ABR by at least 15.2, which was considered M_1 in the noninferiority test setting. Given the large effect size of prophylaxis treatment, an appropriate value for M_2 was considered in order to preserve a sufficiently large proportion of this effect. A value of 2.5 for M_2 (~84% effect preserved) was selected as clinically meaningful for a planned sample size of 60.

Noninferiority Margin for Key Secondary Endpoint (ABR for Spontaneous Bleeds)

The Applicant conducted analyses based on the two BeneFIX studies since the ReFacto study did not utilize this endpoint. Results from the t-test and negative binomial regression were similar with the estimated ABR mean difference of 18.6 and similar 95% CIs. The result from Hodges-

Lehman estimation was larger with 21.8 (16.0, 27.4) for the estimated ABR median difference and its 95% CI.

All analyses indicated that the on-demand ABR was higher than the prophylaxis ABR by at least 13.2, which was considered M_1 in the noninferiority test setting. Given the large effect size of prophylaxis treatment, an appropriate value for M_2 was considered in order to preserve a sufficiently large proportion of this effect. A value of 2.5 for M_2 (~81% effect preserved) was selected as clinically meaningful for a planned sample size of 60.

Noninferiority Margin for Key Secondary Endpoint (ABR for Target Joints Bleeds)

The incidence of target joint bleeds was not an efficacy endpoint in any of the three hemophilia studies in which the estimates for several bleed count endpoints were derived. In the absence of internal data, the Applicant relied on the results of emicizumab publications of HAVEN1 and HAVEN3 studies. The Applicant assumed that the ratio of the effect expressed as the difference between the on-demand treatment versus emicizumab in target joint bleeds over that in joint bleeds would be applicable to characterize the marstacimab effect of the same endpoints. The effect in target joint bleeds is consistently 49% of that in joint bleeds. Therefore, the noninferiority margin of 1.2, derived as 49% of the margin of 2.5 for the joint bleeds, was selected for target joint bleeds, expecting that a similar magnitude (~84%) of the effect would be preserved.

Table 101. Estimated Effect of Target Joint Bleeds and Joint Bleeds From Emicizumab Studies

Mean Difference	HAVEN1	HAVEN3*
	(inhibitors)	(non-inhibitors)
Target joint bleeds	2.9	12.4
Joint bleeds	5.9	25.4
ratio	0.49	0.49

Source: Study B7841005 SAP v6 dated January 31, 2023, Appendix Table A4.2.1.3

* difference between the on-demand treatment and the emicizumab once-weekly group

Abbreviation: SAP, statistical analysis plan

In the Applicant's derivation of NI margin for target joint bleeds endpoint, both inhibitor and noninhibitor populations were used to provide a more stable estimate of the ratio. If only noninhibitor participants were considered (HAVEN 3), there would have no change in NI margin for target joint bleeds.

Noninferiority Margin for Key Secondary Endpoint (ABR for Total Bleeds)

The incidence of target joint bleeds was not an efficacy endpoint in any of the three hemophilia studies in which the estimates for several bleed count endpoints were derived. In the absence of internal data, the Applicant relied on the results of emicizumab publications of HAVEN1 and HAVEN3 studies. The Applicant assumed that the ratio of the effect expressed as the difference between the on-demand treatment versus emicizumab in total bleeds over that in treated bleeds would be applicable to characterize the marstacimab effect of the same endpoints. The effect in total bleeds exceeds 12% to 23% that in treated bleeds, resulting in the geometric mean of a 17% increase. Therefore, the noninferiority margin of 2.9, derived as 117% of the margin of 2.5 for

the treated bleeds, was selected for total bleeds expecting that a similar magnitude (~85%) of the effect would be preserved.

Table 102. Estimated Effect of Treated Bleeds and All Bleeds From Emicizumab Studies

Mean Difference	HAVEN1	HAVEN3*
	(inhibitors)	(non-inhibitors)
All bleeding	22.8	45.1
Treated bleeding	20.4	36.7
Ratio	1.12	1.23

Source: Study B7841005 SAP v6 dated January 31, 2023, Appendix Table A4.2.1.4

* difference between the on-demand treatment and the emicizumab once-weekly group

Abbreviation: SAP, statistical analysis plan

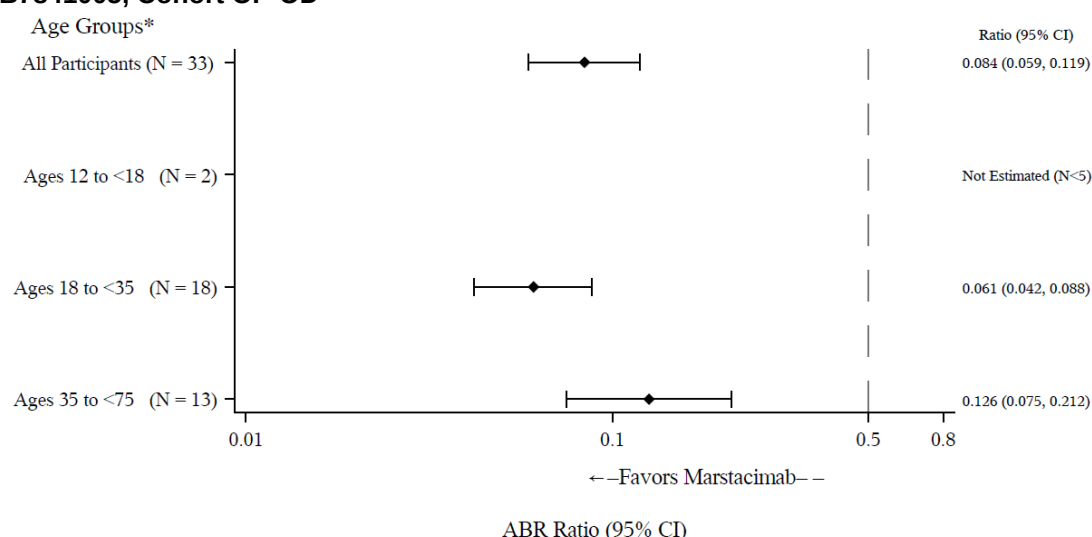
In the Applicant's derivation of NI margin for total bleeds endpoint, both inhibitor and noninhibitor populations were used to provide a more stable estimate of the ratio. However, if only the noninhibitor participants were considered (HAVEN3), the updated NI margin would be higher (3.1) as derived as 123% of the margin 2.5.

16.2. Subgroup Analyses Results by Age, Race, Ethnicity, and Geographical Region

Subgroup analysis results for the primary endpoint (ABR of treated bleeds) by further refined age, race, ethnicity and geographical regions for Cohort OP-OD and Cohort OP-PPX are shown below ([Figure 44](#) through [Figure 49](#)).

By Further Refined Age

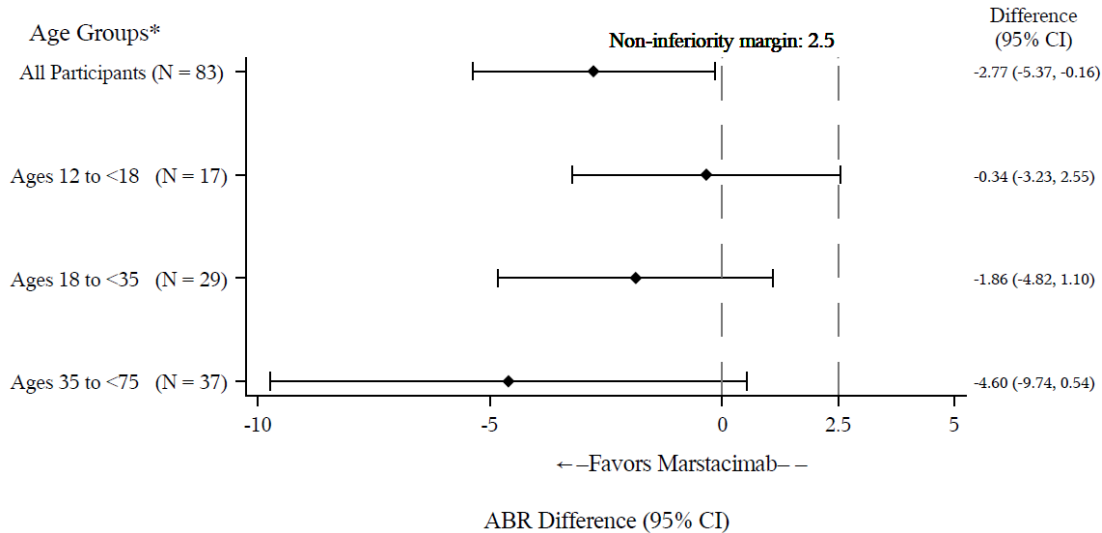
Figure 44. Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Age Group, Study B7841005, Cohort OP-OD



Source: Applicant's responses to AOM discussion, received on November 17, 2023; FDA-verified

* The cutoff age of 35 years is the median age of adult participants across the on-demand and routine prophylaxis groups.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

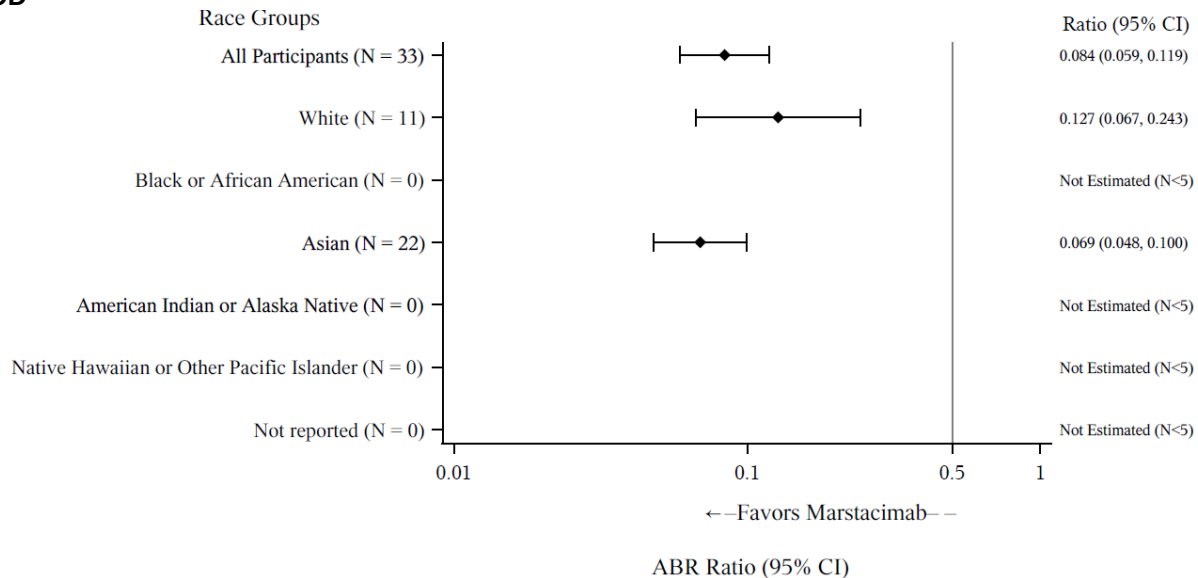
Figure 45. Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Age Group, Study B7841005, Cohort OP-PPX

Source: The Applicant's responses to the AOM discussion received on November 17, 2023; FDA-verified

* The cutoff age of 35 years is the median age of adult participants across the on-demand and routine prophylaxis groups.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

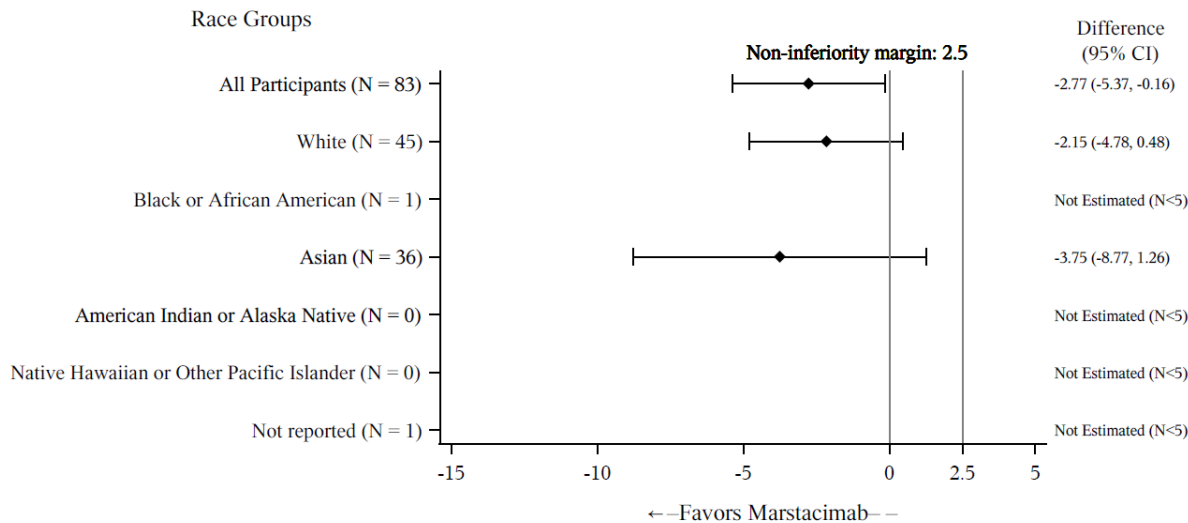
By Race

Figure 46. Comparison of ABRs for Treated Bleeds by Race Groups, Study B7841005, Cohort OP-OD

Source: Study B7841005 Interim Clinical Study Report, Figure 14.2.1.1.9; FDA-verified

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

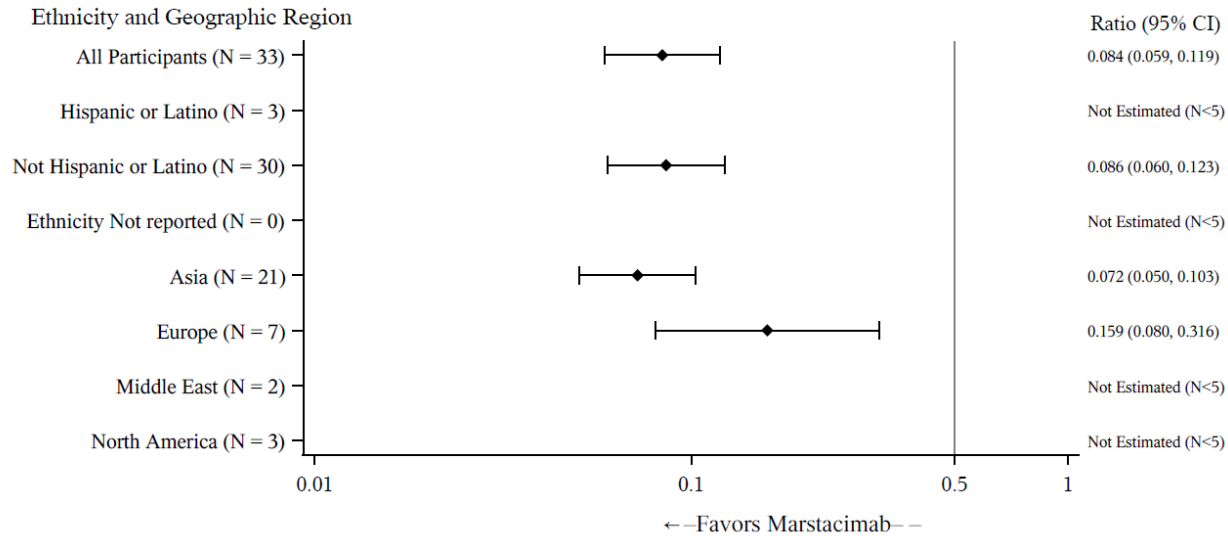
Figure 47. Comparison of ABRs for Treated Bleeds by Race Groups, Study B7841005, Cohort OP-PPX



Source: Study B7841005 Interim Clinical Study Report, Figure 14.2.2.1.9; FDA-verified
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

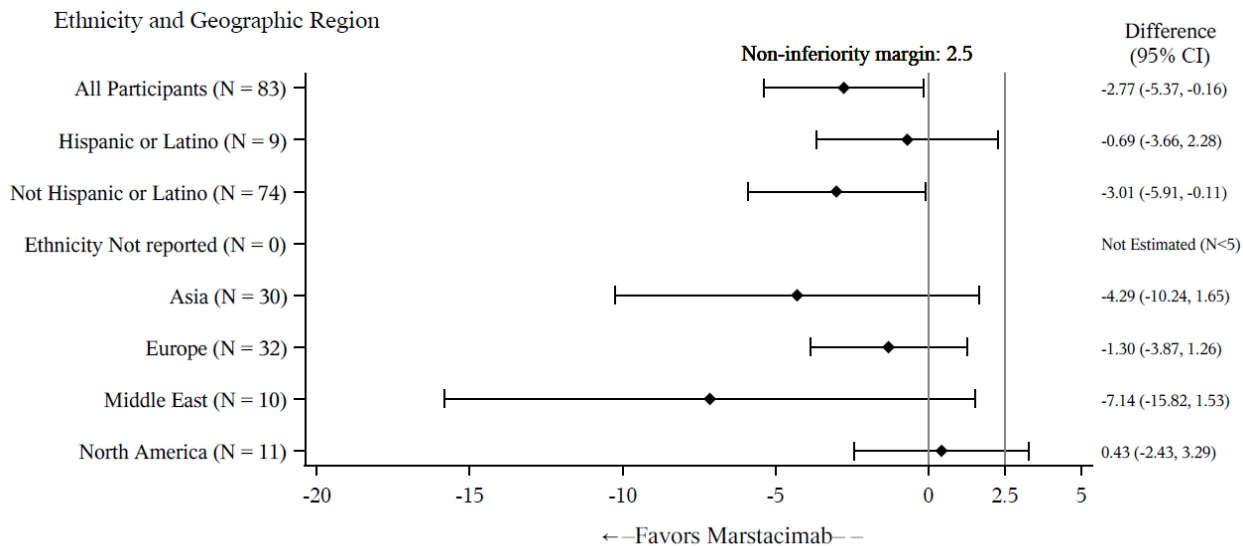
By Ethnicity and Geographic Region

Figure 48. Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Ethnicity and Geographic Region, Study B7841005, Cohort OP-OD



Source: Study B7841005 Interim Clinical Study Report, Figure 14.2.1.1.10; FDA-verified
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

Figure 49. Comparison of the Primary Endpoint (ABR of Treated Bleeds) by Ethnicity and Geographic Region, Study B7841005, Cohort OP-PPX



ABR Difference (95% CI)
Source: Study B7841005 Interim Clinical Study Report, Figure 14.2.2.1.10; FDA-verified
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase

16.3. Supplementary Analysis Results for the Primary Endpoint

Results from the supplementary analyses for handling of intercurrent events (evaluating the impact of preventative infusion and treatment discontinuation) for the primary endpoint for OP-OD and OP-PPX cohorts are presented in [Table 103](#) and [Table 104](#), respectively.

Table 103. Supplementary Analyses of the Primary Endpoint (ABR for Treated Bleeds), Study B7841005, Cohort OP-OD

Supplementary Analysis Type	Estimated ABR Ratio: Marstacimab/On-Demand	95% CI
To assess the impact of preventative infusion		
Including bleeding during preventative infusion	0.083	(0.058, 0.118)
To assess impact of treatment discontinuation or potentially missing bleeding records (N=1)		
Imputing the portion after treatment discontinuation using the mean ABR calculated during treatment and during dosing gap using the mean ABR before and after the dosing gap	0.082	(0.058, 0.117)
Tipping point analysis (tipping multiplier: 154)	0.172	(0.060, 0.497)

Source: updated based on Study B7841005 Interim Clinical Study Report, Table 10

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OD, on-demand; OP, observational phase

Table 104. Supplementary Analyses of the Primary Endpoint (ABR for Treated Bleeds), Study B7841005, Cohort OP-PPX

Supplementary Analysis Type	Estimated ABR Difference: Marstacimab – Factor Prophylaxis	95% CI
To assess the impact of preventative infusion		
Including bleeding during preventative infusion	-2.82	(-5.43, -0.20)
To assess impact of treatment discontinuation or potentially missing bleeding records (N=6)		
Imputing the portion after treatment discontinuation using the mean ABR calculated during treatment and during dosing gap using the mean ABR before and after the dosing gap	-3.12	(-5.73, -0.51)
Tipping point analysis (tipping multiplier: 4.6)	-1.23	(-5.00, 2.53)

Source: updated based on Study B7841005 Interim Clinical Study Report, Table 25

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; N, overall number of participants; OP, observational phase; PPX, prophylaxis

16.4. Results for Superiority Over Factor Prophylaxis

As noted in Section 6.2.1.4 with the discussion of hierarchical testing and multiple testing strategies, the review team considered Study B7841005 noninhibitor cohorts as the equivalent of independent substudies, and individual alpha (0.05) could be tested to each cohort for superiority versus on-demand factor and noninferiority/superiority versus factor prophylaxis separately. The results of the analysis of superiority versus factor prophylaxis did not contribute to the Agency’s regulatory decision and are therefore not included in Section 6. The results of the superiority over factor prophylaxis analysis are presented here for completeness.

Table 105 presents the results for parametric and nonparametric analyses for the primary (ABR treated bleeds) and key secondary ABR endpoints. For the primary endpoint, the Wilcoxon signed rank test had a large p-value of 0.0788 (versus 0.0376 based on the parametric method, that is, the negative binomial regression model). Similarly, for the secondary endpoint ABR of total bleeds, the Wilcoxon signed rank test had a large p-value of 0.0573 (versus 0.0406 based on the negative binomial regression model). The results for the treated bleeds and total bleeds showed nominally statistical significance for superiority over routine prophylaxis but not in the results based on the Wilcoxon signed rank test. In addition, the small nominal p-values for the treated bleeds and total bleeds may be due to extreme high ABRs during the OP in the HA population. The results for other types of bleeds (spontaneous bleeds, joint bleeds, and target joint bleeds) were nominally not statistically significant for superiority over routine prophylaxis regardless of the parametric and nonparametric methods were used.

The review team acknowledged that the nonparametric test could be less powerful and thus had larger p-values. However, overall, the results were determined not to be robust because parametric and nonparametric methods reached different conclusions. Therefore, the superiority over routine prophylaxis could not be claimed.

Table 105. Summary of Parametric and Nonparametric Analyses Results for the Primary and Key Secondary Endpoints, Study B7841005, Cohort OP-PPX (N=83)

		Negative Binomial Regression ¹	Wilcoxon (NI) ²	Wilcoxon (Sup) ³
Endpoints				
Primary	Treated bleeds	0.0376	<0.0001	0.0788
	Spontaneous bleeds	0.0566	<0.0001	0.0972
	Joint bleeds	0.1680	<0.0001	0.4085
Secondary	Total bleeds	0.0406	<0.0001	0.0573
	Target joint bleeds	0.2811	<0.0001	0.4655

Source: summarized based on the Applicant’s CSR and IR responses received on February 15, 2024; FDA-verified

¹ P-value based on negative binomial for null hypothesis of mean difference=0

² P-value based on Wilcoxon signed rank test for the null hypothesis that the median ABR difference=2.5 for noninferiority

³ P-value based on Wilcoxon signed rank test for the null hypothesis that the median ABR difference=0 for superiority

Abbreviations: ABR, annualized bleeding rate; CSR, clinical study report; IR, information request; N, overall number of participants; NI, noninferiority; OP, observational phase; PPX, prophylaxis; sup, superiority

16.5. Sensitivity Analysis for Extreme Values

[Figure 50](#) shows the distribution of ABRs for participants in cohort OP-PPX by hemophilia type. For HA and HB, the distribution is shown for OP (lower graph) and ATP (upper graph). As seen in the figure, the distributions of the primary endpoint (ABR for treated bleeds) for HA and HB populations are different. The range of ABRs is wider in HA participants compared to HB participants. This would be expected as the HA phenotype is generally more severe than HB phenotype, and so higher ABRs would be expected both in the OP and the ATP. However, in Study B7841005, for the HA population, the distribution tail, with several extreme values, is longer for the OP compared to the ATP. In contrast in the HB population, the tail, with several extreme values, is longer in ATP compared to OP.

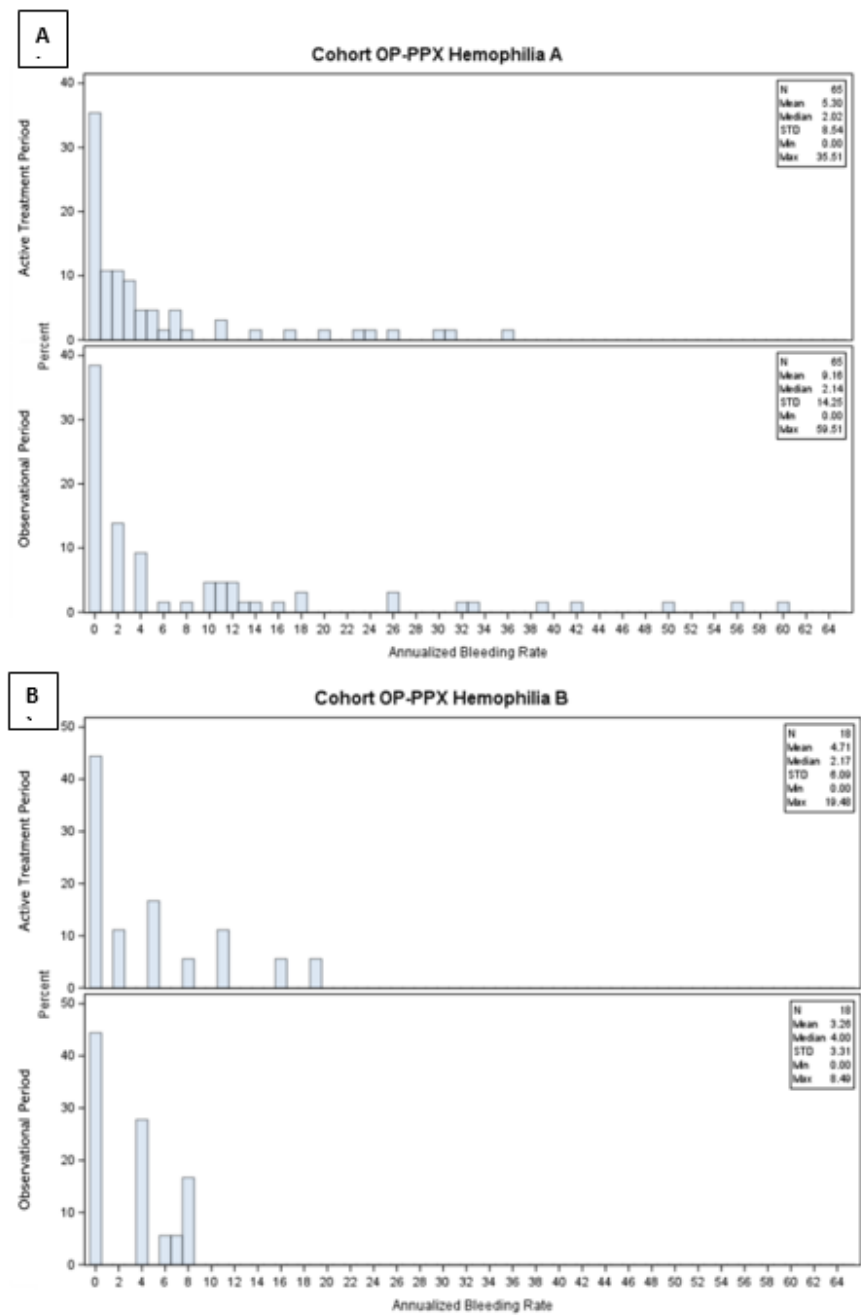
When there are extreme values in the ATP not seen in the OP, as with the HB population, the mean difference of the ABR is pushed higher, suggesting poorer bleeding control with marstacimab prophylaxis compared to factor prophylaxis. This is discussed as a key efficacy issue in [Section 6.3.1](#). When there are extreme values in the OP not seen in the ATP, as with the HA population, the mean difference of the ABR is pushed lower, suggesting poorer bleed control with factor prophylaxis compared to marstacimab prophylaxis. This can be due to poor compliance with the OP or chance.

To assess the robustness of the final results and assay sensitivity for extreme values (ABR > 40 for HA, ABR > 10 for HB), the Applicant, at the request of the Agency, conducted additional sensitivity analyses for the primary endpoint using the Negative Binomial Regression Model and Wilcoxon Signed Rank test, using different imputation methods (mean, median, and zero ABR imputation) for extreme ABRs. Specifically, imputations were requested using different cutoffs to determine extreme ABRs considering HA and HB separately and HA and HB together. The Applicant conducted the requested analyses by imputing the mean (or median) from the remaining (non-imputed) participants based on the pooled HA and HB populations.

According to the Applicant's analysis results, non-inferiority vs factor prophylaxis was met for all imputation methods for all scenarios. However, the review team determined this approach, which pools HA and HB ABRs in calculating the imputed value, may not be appropriate given the differences in the ranges of the ABR distributions between HA and HB. Thus, the review team conducted additional, more conservative, sensitivity analyses by replacing the extreme ABRs by mean (or median) of the ABRs of remaining participants with the corresponding hemophilia A (or B) type. That is, extreme HA ABRs are replaced by the mean (median) ABR of the remaining HA participants and HB ABRs are replaced by the mean (median) ABR of the remaining HB participants. Non-inferiority versus factor prophylaxis was also met for all scenarios using these imputation methods.

In conclusion, these additional sensitivity analyses using parametric and non-parametric analyses with different imputation methods for extreme ABRs in HA and HB populations supported the final results for noninferiority versus factor prophylaxis for the primary endpoint (ABR for treated bleeds).

Figure 50. ABR Treated Bleed Frequency Distribution by Phase, Hemophilia A and Hemophilia B, Study B784005, Cohort OP-PPX



Source: Reviewer Table
Abbreviations: N, overall number of participants; STD, standard deviation; Mn, minimum; Max, maximum

17. Clinical Safety

17.1. Assessment of Safety by Observation Period Treatment (Factor On-Demand, Factor Prophylaxis)

In Section 6.3, the safety analysis pooled the OP-OD and OP-PPX cohorts. This was done because both cohorts received factor replacement during OP with the only difference being frequency of administration (on-demand versus prophylaxis) and all participants, regardless of observational phase treatment, received the same ATP marstacimab regimen; therefore, the treatment received prior to enrollment and during OP is not expected to impact the safety profile of marstacimab overall.

The demographics and baseline disease characteristics are shown in Table 106. There are differences in the age distribution between the two cohorts. A higher percentage of participants were <18 years of age in the OP-PPX cohort (21%) compared to the OP-OD cohort (6%); however, a higher percentage of participants in the OP-OD cohort were 18 to 44 years of age (82%) compared to the OP-PPX cohort (52%). There are differences in site enrollment between the two cohorts, most notably, a higher percentage of participants in the OP-OD cohort were enrolled in Asia (64%) compared to the OP-PPX cohort (36%). This likely reflects standard treatment practices (on-demand versus prophylaxis use of factor) in different regions. There are some differences in number of baseline number of target joints, notably, a higher proportion of participants with ≥ 3 target joints in the OP-OD cohort (36%) compared to OP-PPX (16%). This may reflect effectiveness of factor prophylaxis compared to factor OD.

Table 107 provides an overview of frequency analysis of safety during the ATP with marstacimab in Study B7841005, by cohort. The overall rate of treatment-emergent adverse events (TEAEs) was higher in the OP-PPX (75%), compared to the OP-OD; however, this is primarily accounted for by an increase in mild events in the OP-PPX. While all SAEs occurred in the OP-PPX, as noted in Section 7.6.1.3, all but one of the SAEs reported in the primary safety population during the ATP for Study 7684015 were assessed as not related to marstacimab.

The difference in frequency for TEAEs based on FMQ (narrow) (Table 108) between cohorts was <10% for all FMQs (narrow) with the exception of viral infection, which occurred in 27% of participants in the OP-PPX cohort compared to 6% in the OP-OD cohort, and hemorrhage, which occurred in 13% of participants in the OP-PPX cohort compared to 3% in the OP-OD cohort. The higher frequency of viral infections in the OP-PPX cohort may reflect a slightly older population or may be due to chance, but based on mechanism of action is unlikely to be due to marstacimab. The event of hemorrhage is related to underlying disease.

Based on a comparison of safety profiles in the OP-OD and OP-PPX cohorts, the review team concluded that there were no clinically meaningful differences and reporting in the United States Prescribing Information (USPI) by prior factor therapy (i.e., by cohort) was not needed to support the safe and effective use of marstacimab.

Table 106. Demographics and Baseline Disease Characteristics by Cohort and Overall, Primary Safety Population, Study B7841005

Characteristic	Overall N=116	OP-OD (N=33)	OP-PPX (N=83)
Sex, n (%)			
Male	116 (100)	33 (100)	83 (100)
Age, years			
Mean (SD)	31.9 (13.8)	31.9 (11.04)	32.6 (14.81)
Median (min, max)	29 (12, 66)	29 (15, 58)	31 (13, 66)
Age group, years, n (%)			
<18	19 (16.4)	2 (6.1)	17 (20.5)
18 to 44	70 (60.3)	27 (81.8)	43 (51.8)
45 to 64	26 (22.4)	4 (12.1)	22 (26.5)
65 to 74	1 (0.9)	0	1 (1.2)
Race, n (%)			
Asian	58 (50.0)	22 (66.7)	36 (43.4)
Black or African American	1 (0.9)	0	1 (1.2)
White	56 (48.3)	11 (33.3)	45 (54.2)
Missing	1 (0.9)	0	1 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	12 (10.3)	3 (9.1)	9 (10.8)
Not Hispanic or Latino	104 (89.7)	30 (90.9)	74 (89.2)
Baseline eGFR (mL/min/1.73m ²), n (%)			
≥90	91 (78.4)	29 (87.9)	3 (75)
≥60 to <90	23 (19.8)	4 (12.1)	19 (22.9)
Hemophilia type, n (%)			
Hemophilia A	91 (78.5)	26 (78.8)	65 (78.3)
Hemophilia B	25 (21.5)	7 (21.2)	18 (21.7)
ISTH disease severity, n (%)			
Moderate	0	0	0
Severe	116 (100)	33 (100)	83 (100)
Number of target joints at baseline, n (%)			
0	36 (31)	0	36 (43.4)
1	26 (22.4)	7 (21.2)	19 (22.9)
2	29 (25)	14 (42.4)	15 (15.1)
≥3	25 (21.6)	12 (36.4)	13 (15.7)
Geographical region, n (%)			
Asia	51 (44)	21 (63.6)	30 (36.1)
Europe	39 (33.6)	7 (21.2)	32 (38.6)
Middle East	12 (10.3)	2 (6.1)	10 (12)
North America (Canada, Mexico, U.S.)	14 (12.1)	3 (9.1)	11 (13.3)

Source: FDA table Study B7841005 adsl

Abbreviations: eGFR, estimated glomerular filtration rate; ISTH, International Society on Thrombosis and Haemostasis, Inc; max, maximum; min, minimum; N, overall number of participants; n, number of participants in subgroup; OD, on-demand; OP, observational phase; PPX, prophylaxis; SD, standard deviation; U.S., United States

Table 107. Overview of Adverse Events, by Cohort and Overall, Active Treatment Phase, Primary Safety Population, Study B7841005

Parameter	Overall (N=116) n (%)	OP-OD (N=33) n (%)	OP-PPX (N=83) n (%)
Treatment-emergent adverse events	74 (64)	12 (36)	62 (75)
Severe and worse	6 (5.2)	0	6 (5.2)
Moderate	17 (14.7)	3 (9.1)	14 (16.9)
Mild	51 (44)	9 (27.3)	42 (50.6)
TEAE leading to death	0 (0)	0 (0)	0 (0)
Serious TEAEs	7 (6)	0 (0)	7 (8.4)
TEAE leading to permanent discontinuation	1 (0.9)	0 (0)	1 (1.2)
TEAE leading to interruption	15 (12.9)	1 (3)	14 (17)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

Duration is 12 months in the active treatment phase.

Severity as assessed by the investigator.

Abbreviations: N, number of patients in treatment arm; n, number of patients with at least one event; OD, on-demand; OP, observational phase; PPX, prophylaxis; TEAE, treatment-emergent adverse event

Table 108. Frequency (≥2%) of Treatment-Emergent Adverse Events by System Organ Class and FMQ (Narrow), by Cohort and Overall, Active Treatment Phase, Primary Safety Population, Study Study B7841005

System Organ Class Preferred Term	Overall N=116 n (%)	OP-OD N=33 n (%)	OP-PPX N=83 n (%)
Blood and lymphatic system disorders (SOC)			
Anemia	2 (1.7)	0	2 (2.4)
Cardiac disorders (SOC)			
Systemic hypertension	5 (4.3)	1 (3.0)	4 (4.8)
Arrhythmia	1 (0.9)	0	1 (1.2)
Gastrointestinal disorders (SOC)			
Diarrhea	2 (1.7)	0	2 (2.4)
General disorders and administration site conditions (SOC)			
Local administration reaction	13 (11.2)	2 (6.1)	11 (13.3)
Fall	2 (1.7)	0	2 (2.4)
Fatigue	2 (1.7)	1 (3.0)	1 (1.2)
Peripheral edema	2 (1.7)	0	2 (2.4)
Pyrexia	2 (1.7)	0	2 (2.4)
Infections and infestations (SOC)			
Viral infection	24 (20.7)	2 (6.1)	22 (26.5)
Nasopharyngitis	10 (8.6)	3 (9.1)	7 (8.4)
Bacterial infection	4 (3.4)	0	4 (4.8)
Metabolism and nutrition disorders (SOC)			
Lipid disorder	3 (2.6)	0	3 (3.6)
Musculoskeletal and connective tissue disorders (SOC)			
Arthralgia	3 (2.6)	0	3 (3.6)
Fracture	3 (2.6)	0	3 (3.6)
Arthritis	2 (1.7)	0	2 (2.4)
Back pain	2 (1.7)	0	2 (2.4)
Tendinopathy	2 (1.7)	0	2 (2.4)
Nervous system disorders (SOC)			
Headache	8 (6.9)	1 (3.0)	7 (8.4)

System Organ Class Preferred Term	Overall N=116 n (%)	OP-OD N=33 n (%)	OP-PPX N=83 n (%)
Psychiatric disorders (SOC)			
Anxiety	2 (1.7)	0	2 (2.4)
Skin and subcutaneous tissue disorders (SOC)			
Pruritus	8 (6.9)	2 (6.1)	6 (7.2)
Erythema	3 (2.6)	0	3 (3.6)
Rash	2 (1.7)	0	2 (2.4)
Vascular disorders (SOC)			
Hemorrhage	12 (10.3)	1 (3.0)	11 (13.3)

Source: adae.xpt; Software: R

Safety set is defined as those participants who received at least one dose of marstacimab during the active treatment phase.

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period

Active treatment phase is 12 months.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; OD, on-demand; OP, observation phase; PPX, prophylaxis; PT, preferred term; SOC, system organ class

17.2. Assessment of Safety by Hemophilia Type

In Section 6.3, the primary safety population includes participants with HA and HB. Based on the similarity of the underlying mechanism of HA and HB and the mechanism of action of marstacimab, Study B7841005 does not enroll participants HA and HB to separate cohorts. The safety profile is not expected to be different in these two subpopulations.

Table 109 provides a frequency-based overview of TEAEs by hemophilia type reported in the safety population during the active treatment phase for Study B7841005. Overall, the analysis of TEAEs by hemophilia type showed no significant differences in the frequency of adverse events between the two groups (HA versus HB). As noted above, only one SAE was assessed as related to marstacimab, and therefore, analysis of SAEs by subgroup is not meaningful. Table 110 presents the most common TEAEs by system organ class (SOC) and preferred term (PT) and hemophilia type. There are no significant differences in frequency for any specific PT or SOC between HA and HB.

Based on this subgroup analysis, the review team concludes that reporting in the USPI by hemophilia subtype not needed for the safe and effective use of marstacimab.

Table 109. Overview of Adverse Events by Hemophilia Type, Active Treatment Phase, Safety Population, Study B7841005

Parameter	Hemophilia A N=91 n (%)	Hemophilia B N=25 n (%)
Treatment-emergent adverse events, n (%)	57 (62.6)	17 (68)
Severe and worse	4 (4.4)	2 (8)
Moderate	13 (14.3)	4 (16)
Mild	40 (44)	11 (44)
TEAE leading to death, n (%)	0	0
Serious TEAEs, n (%)	6 (6.6)	1 (4)
TEAE leading to permanent discontinuation, n (%)	1 (1.1)	0
TEAEs leading to temporal discontinuation, n (%)	11 (12.1)	4 (16)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period
Duration is 12 months in the active treatment phase.

Abbreviations: N, number of participants in treatment arm; n, number of participants with adverse event; TEAE, treatment-emergent adverse event

Table 110. Common Adverse Events, Occurring in ≥2% of Participants, by Preferred Term, by Hemophilia Type, Active Treatment Phase, Primary Safety Population, Study B7841005

Parameter	Hemophilia A N=91 n (%)	Hemophilia B N=25 n (%)
Any AE	57 (62.6)	17 (68)
COVID-19	16 (17.6)	4 (16)
Dental caries	4 (4.4)	0
Headache	4 (4.4)	3 (12)
Injection site pruritus	4 (4.4)	0
Hypertension	3 (3.3)	2 (8)
Injection site erythema	3 (3.3)	0
Pruritus	3 (3.3)	1 (4)
Tonsillitis	3 (3.3)	1 (4)
Upper respiratory tract infection	3 (3.3)	0
Arthralgia	2 (2.2)	1 (4)
Contusion	2 (2.2)	3 (12)
Fatigue	2 (2.2)	0
Fibrin D dimer increased	2 (2.2)	1 (4)
Hemorrhoids	2 (2.2)	1 (4)
Head injury	2 (2.2)	0
Herpes zoster	2 (2.2)	0
Injection site pain	2 (2.2)	0
Pain in extremity	2 (2.2)	0
Peripheral swelling	2 (2.2)	0
Prothrombin fragment 1.2 increased	2 (2.2)	1 (4)
Pyrexia	2 (2.2)	0
Rhinitis allergic	2 (2.2)	0
Pharyngitis	0	2 (8)
Rhinitis	0	2 (8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any adverse event that started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.
Duration is 12 months for active treatment phase.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; MedDRA, Medical Dictionary for Regulatory Activities;
N, number of participants in treatment arm; n, number of participants with adverse event

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action / Drug Resistance

Not applicable.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A clinical inspection summary for BLA 761369 was completed by the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations with a final signature date of August 1, 2024. Four clinical sites were inspected for Study B7841005 (Site 1123 [Nirmal Kumar Choraria, MD (Surat, Gujarat India)], Site 1035 [Young Shil Park, MD (Seoul, South Korea)], Site 1127 [Javier Morales Adrian, MD (Merida, Yucatan, Mexico) and Site 1013 [Laurent Frenzel, MD (Paris,France)]).

The Office of Scientific Investigations concluded that, based on the inspections, the study data derived from these four clinical sites are considered reliable and are acceptable. The study data submitted to the Agency for assessment appears acceptable in support of the proposed indication.

Protocol Deviations

Study B7841005

The Application provided a listing of protocol deviations. A summary of deviations classified as “important protocol deviations” reported is presented in [Table 111](#). Of note, dosing administration error occurred in 20% of participants across the cohorts (n=22). This occurred only once in each of the participants and were assessed as having no impact on overall efficacy or safety findings of the study.

Study Site 1053 (Monterrey, Mexico) was terminated by the Applicant on March 2022, due to significant noncompliance of Good Clinical Practice (GCP) leading to missing and unverified data noted during the conduct of the study. This site screened a total of four

HYMPAVZI (marstacimab-hncq) injection

participants: three participants failed screening and 1 adolescent participant was administered marstacimab but discontinued from treatment when study conduct at this site was terminated. No deaths were reported. All data from participants at this site were maintained in the clinical database but excluded from the clinical study report data analysis.

Table 111. Summary of Important Protocol Deviations, Study B7841005

Protocol Deviation Coded Term/ Protocol Deviation Term	OP-OD N=33 n (%)	OD-PPX N=83 n (%)	Population N=116 n (%)
Participants with at least 1 protocol deviation	10 (30.3)	56 (67.5)	66 (56.9)
Procedures/tests	6 (18.2)	24 (28.9)	30 (25.9)
PRO questionnaires not completed	4 (12.1)	19 (22.9)	23 (19.8)
Completed incorrect PRO questionnaire(s) for participant age group	2 (6.1)	8 (9.6)	10 (8.6)
Participant did not complete the eDiary as instructed	1 (3)	1 (1.2)	2 (1.7)
Investigational Product	4 (12.1)	22 (26.5)	26 (22.4)
Dosing/administration error	2 (6.1)	21 (25.3)	23 (19.8)
Participant met dose escalation criteria and increased dose decision implemented by Investigator without consultation with Sponsor medical monitor	1 (3)	2 (2.4)	3 (2.6)
Participant did not maintain 80% compliance with study drug during ATP	1 (3)	0	1 (0.9)
Concomitant Medications	3 (9.1)	20 (24.1)	23 (19.8)
Participant did not adhere to protocol-specified washout period prior to V7	1 (3)	10 (12)	11 (9.5)
Took prohibited concomitant medication/vaccine	1 (3)	7 (8.4)	8 (6.9)
Hemophilia product change occurred during study without consultation and agreement with Sponsor medical monitor, prior to implementation	1 (3)	2 (2.4)	3 (2.6)
Participant was not at least 80% compliant with hemophilia treatment prophylaxis regimen during observational phase	0	2 (2.4)	2 (1.7)
Took permitted concomitant medication/vaccine, but not as specified per protocol	0	1 (1.2)	1 (0.9)
Informed Consent (IC), n (%)	1 (3)	17 (20.5)	18 (15.5)
IC had not undergone proper Pfizer approval	0	6 (7.2)	6 (5.2)
Revised IC not signed at the first participant visits after the revised/approved IC was available at site	1 (3)	4 (4.8)	5 (4.3)
Participant did not sign the IC but gave verbal consent	0	4 (4.8)	4 (3.4)
Participant signed a superseded/outdated version of the IC	0	2 (2.4)	2 (1.7)
Participant did not sign consent at age of majority	0	1 (1.2)	1 (0.9)
Participant signed consent but did not date it	0	1 (1.2)	1 (0.9)
Safety Reporting	1 (3)	7 (8.4)	8 (6.9)
Study drug not temporarily interrupted in participant with symptomatic COVID-19	1 (3)	3 (3.6)	4 (3.4)
SAE not reported to Sponsor within specified timeframe	0	3 (3.6)	3 (2.6)
Medication error not reported to the Sponsor within 24 hours of investigator's awareness	0	1 (1.2)	1 (0.9)
Laboratory	0	4 (4.8)	4 (3.4)
Immunogenicity samples not collected	0	4 (4.8)	4 (3.4)

Protocol Deviation Coded Term/ Protocol Deviation Term	OP-OD N=33 n (%)	OD-PPX N=83 n (%)	Population N=116 n (%)
Inclusion/exclusion	1 (3)	1 (1.2)	2 (1.7)
Participant did not meet inclusion criteria for noninhibitor cohort per protocol	1 (3)	0	1 (0.9)
Subject did not meet inclusion criteria for hemophilia A or B severity	0	1 (1.2)	1 (0.9)
Randomization	0	1 (1.2)	1 (0.9)

Source: ADDV.xpt; Software: R

Duration is observational phase: 6 months; active treatment phase: 12 months.

Abbreviations: ATP, active treatment phase; COVID-19, coronavirus disease of 2019; IC, informed consent; mITT, modified intent-to-treat; N, number of participants in treatment arm; n, number of participants in specified population or group; OP, observational phase; PRO, patient-reported outcome; SAE, serious adverse event; V7, visit 7

Review protocol deviations we concluded that deviations are unlikely to have had an impact on results.

23. Labeling: Key Changes and Considerations

This United States Prescribing Information (USPI) review includes a high-level summary of the rationale for major changes to the finalized USPI as compared to the Applicant's draft USPI (Table 112). The USPI was reviewed to ensure that USPI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 112. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized USPI ² Compared to Applicant's Draft USPI
BOXED WARNING	No Boxed Warning
1 INDICATIONS AND USAGE	Revised "adults" to "adult" to include them in the patient's group.
	2.1 Revised to place recommended dosage as first subsection. Added text to describe approach for missed doses and splitting doses into two injection sites if needed.
	2.2 Revised subheading to Preparation and Administration.
2 DOSAGE AND ADMINISTRATION	2.3 Revised "switching" to "changing" as switching text is usually for biosimilar products. Added text to describe lack of data in patients changing from non-factor-based hemophilia treatments to HYMPAVZI.
	2.6 Added "Pregnancy Testing" subsection due to risks of embryofetal toxicity.
4 CONTRAINDICATIONS	No change.
	5.1 Thromboembolic Events: Revised to describe class risks due to mechanism of action, remove reference to (b) (4) and unsupported claims (b) (4)
5 WARNINGS AND PRECAUTIONS	5.2 Hypersensitivity: Revised for clarity, relocated less serious risks to section 6.
	Added 5.3 Embryofetal Toxicity warning based on Mechanism of Action.

Full PI Sections ¹	Rationale for Major Changes to Finalized USPI ² Compared to Applicant's Draft USPI
6 ADVERSE REACTIONS	6.1 Removed reference to (b) (4) Based the safety on the BASIS study. Added description of the dosing. Added exposure information. Removed (b) (4)
7 DRUG INTERACTIONS	Removed text (b) (4) and added information on the lack of laboratory test interference for aPTT and PT; which would be useful for clinicians to know.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Revised 8.1 Pregnancy to be consistent with the FDA draft guidance for industry <i>Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format</i> (July 2020) and current labeling practices. Based the risk of embryofetal harm on mechanism of action. Revised 8.2 Lactation to be consistent with the PLLR guidance and current labeling practices (July 2020). Added information regarding the presence of IgG and moAbs in human milk. 8.3 Females and Males of Reproductive Potential revised to reflect risk of fetal harm and the use of pregnancy testing prior to initiation of treatment. Recommended the use of contraception for female patients for at least 2 months after the last dose as not all product will be eliminated by 30 days. 8.4 Pediatric Use. Revised the pediatric use statement to be consistent with the FDA draft guidance for industry <i>Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice</i> (March 2019). Added the basis for approval in pediatric patients. 8.5 Geriatric Use revised to be consistent with the FDA draft guidance for industry <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (September 2020).
9 DRUG ABUSE AND DEPENDENCE	n/a
10 OVERDOSAGE	Removed (b) (4) as it was not consistent with 21CFR 201.57(c)(11).
12 CLINICAL PHARMACOLOGY	Revised entire section to be consistent with the FDA guidance for industry <i>Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format</i> (December 2016). 12.1 Mechanism of Action: Revised to provide just the established MoA. Removed vague descriptors such as (b) (4) 12.2 Pharmacodynamics: Revised to remove reference to (b) (4) and describe the PD.

Full PI Sections ¹	Rationale for Major Changes to Finalized USPI ² Compared to Applicant's Draft USPI
	12.3 Pharmacokinetics: Revised to be c/w the clinical pharmacology labeling guidance (December 2016) and to reflect data submitted. Added Body Weight and Pediatric Patients subheadings. 12.6 Immunogenicity: Revised to reflect data submitted.
13 NONCLINICAL TOXICOLOGY	Deleted 13.2 to be consistent with 21 FR 201.57(c)(14); text did not reflect information not already reflected in the human data sections.
14 CLINICAL STUDIES	Revised to describe the trial used to establish efficacy (BASIS study). Removed reference to (b) (4) per the FDA guidance for industry <i>Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format</i> (January 2006). Revised presentation of demographics to incorporate required groups. Removed reference to (b) (4). Removed (b) (4). (per the FDA guidance for industry <i>Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims</i> (December 2009)) and lack of statistically significant results. Removed (b) (4).
17 PATIENT COUNSELING INFORMATION	Revised to reflect text in Full USPI.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	3 Dosage Forms and Strengths: removed (b) (4). 11 Description revised to be consistent with 21CFR 201.57(c)(12). Added the Established Pharmacologic Class from Highlights. 16 How Supplied: Revised by removing (b) (4). Storage and Handling: Clarified storage conditions and protection from light.

Source: Generated by the FDA review team from the Applicant's proposed label.

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.

Abbreviations: aPTT, activated partial thromboplastin time; AR, adverse reaction; c/w, consistent with; EPC, established pharmaceutical class; FPI, full Prescribing Information; IgG, immunoglobulin G; MoA, mechanism of action; moAbs, monoclonal antibodies; n/a, not applicable; PD, pharmacodynamic; PLLR, Pregnancy and Lactation Labeling Rule; PI, Prescribing Information; PRO, patient-reported outcome; PT, preferred term

Throughout all sections of labeling, the following edits were made:

- Insertion of the conditionally-approved tradename “HYMPAVZI.”
- Insertion of the FDA-recommended nonproprietary name suffix “-hncq.”
- Revised the use of nonproprietary name vs. tradename as appropriate.
- Replaced passive voice with active voice language.

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- United States Prescribing Information
- Patient package insert
- Instructions for use

24. Postmarketing Requirements and Commitments

None

25. Financial Disclosure

Table 113. Covered Clinical Study, Study B7841005

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 134		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3 investigators		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Source: Reviewer Table based on financial information provide by Applicant
 Abbreviation: FDA, Food and Drug Administration

26. References

26.1. Literature

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26.2. Guidances for Industry

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26.3. Other

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27. Review Team

Table 114. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Courtney Hamilton, Carleveva Thompson
Nonclinical reviewer	Fred Alavi
Nonclinical team leader	Pedro DelValle
OCP reviewer(s)	Yoo Jin Moon, Hui Wei
OCP team leader(s)	Sudharshan Hariharan, Jiang Liu
Clinical reviewer	Saleh Ayache
Clinical team leader	Margaret Thompson
Biometrics reviewer	Qing Xie, Fei Wu
Biometrics team leader	Lola Luo, Yeh-Fong Chen
Cross-disciplinary team leader	Margaret Thompson
Division director (pharm/tox)	Calvin Lee Elmore
Division director (OCP)	Jaya Vaidyanathan
Division director (OB)	Yuan Li Shen
Division director (clinical)	Tanya Wroblewski
Office director (or designated signatory authority)	Lisa Yanoff

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 115. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Chana Fuchs; Kristine Leahy
Microbiology	Max Van Tassell, Liquin Zhao, Wayne Siefert
OPDP	Melissa Khashei
OSI	Anthony Orenca
OSE/DEPI	Kate Gelperin, Steven Bird
OSE/DMEPA	Jody Kundreskas, Mille Shah, Nicole Iverson
OSE/DRISK	Donella Fitzgerald, Jacqueline Sheppard, Mallika Mundkur, Sarah Kang
Other	Helen Young, Barbara Fuller, Janice Ferguson, Shruti Mistry, Virginia Kwitkowski

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-116 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Virginia Kwitkowski Digitally signed by Virginia Kwitkowski Date: 10/10/2024 4:54 PM EDT GUID: 20241010205419				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Virginia Kwitkowski OCHEN DNH	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Virginia Kwitkowski Digitally signed by Virginia Kwitkowski Date: 10/10/2024 4:54 PM EDT GUID: 20241010205451				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Fred Alavi OCHEN DPTCHEN	Sections: 5, 7, 8 and 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Fred Alavi Digitally signed by Fred Alavi Date: 10/10/2024 4:56 PM EDT GUID: 20241010205626				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Other Discipline Primary Reviewer	Hui Wei OCP DPM	Sections: 14.5	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Hui Wei Digitally signed by Hui Wei Date: 10/10/2024 4:57 PM EDT GUID: 20241010205729				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jayabharathi Vaidyanathan		Digitally signed by Jayabharathi Vaidyanathan Date: 10/10/2024 5:07 PM EDT GUID: 2024101021713		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Saleh Ayache OCHEN DNH	Sections: Sections 1, 2, 3, 4, 6, 7, 8.3, 9.1, 10, 11, 15, 17, 22, 25,	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Saleh Ayache		Digitally signed by Saleh Ayache Date: 10/10/2024 5:11 PM EDT GUID: 20241010211149		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Yeh Fong Chen OB DBIX	Sections: 6.2.1, 6.3.1, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yeh Fong Chen Digitally signed by Yeh Fong Chen Date: 10/10/2024 5:16 PM EDT GUID: 2024101021167				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Qing Xie OB DBIX	Sections: 6.2.1, 6.3.1, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Qing Xie Digitally signed by Qing Xie Date: 10/10/2024 5:16 PM EDT GUID: 20241010211649				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Yuan Shen OB DBIX	Sections: 6.2.1, 6.3.1, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yuan Shen Digitally signed by Yuan Shen Date: 10/10/2024 5:17 PM EDT GUID: 20241010211740				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Yoo Jin Moon OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yoo Jin Moon Digitally signed by Yoo Jin Moon Date: 10/10/2024 5:40 PM EDT GUID: 20241010214012				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Sudharshan Hariharan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sudharshan Hariharan Digitally signed by Sudharshan Hariharan Date: 10/10/2024 6:55 PM EDT GUID: 20241010225549				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Margaret Thompson OCHEN DNH	Sections: 1,2,3,4,6,7,10,11,12,1 5, 16, 17,18,19,20, 21,22,23,24, 25,26,27	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Margaret Thompson Digitally signed by Margaret Thompson Date: 10/10/2024 10:19 PM EDT GUID: 202410112192				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Tertiary Reviewer	Tanya Wroblewski OCHEN DNH	Sections: all sections	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tanya Wroblewski Digitally signed by Tanya Wroblewski Date: 10/11/2024 6:33 AM EDT GUID: 2024101110339				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13.1	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore Digitally signed by Calvin Elmore Date: 10/11/2024 9:50 AM EDT GUID: 2024101113500				

BLA 761369

HYMPAVZI (marstacimab-hncq) injection

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Pedro Delvalle OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.3, 8.4, 13.	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Pedro Delvalle Digitally signed by Pedro Delvalle Date: 10/11/2024 9:58 AM EDT GUID: 20241011135812				

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARGARET C THOMPSON
10/10/2024 10:19:29 PM

TANYA M WROBLEWSKI
10/11/2024 10:13:41 AM

LISA B YANOFF
10/11/2024 11:47:57 AM