TITLE PAGE

Protocol 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

Protocol Number: B7841005

Amendment Number: 7

Compound Number: PF-06741086

Study Phase: Phase 3

Short Title: PROPHYLAXIS STUDY OF PF-06741086 IN ADOLESCENT AND ADULT HEMOPHILIA PARTICIPANTS WITH OR WITHOUT INHIBITORS

Acronym: Not applicable

Sponsor Name: Pfizer Inc.

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	**ID**
US IND Number:	126734
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ClinicalTrials.gov ID:	NCT03938792

Approval Date: 24 March 2022

Protocol Amendment Summary of Changes Table

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

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Amendment 7, 24 March 2022

The amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:

The protocol was amended:

a) to remove the Interim Analysis for futility within each participant population of interest (ie, Inhibitor Cohort with prior on-demand therapy; Non-Inhibitor Cohort with prior on-demand therapy; Non-Inhibitor Cohort with prior prophylaxis) planned after 50% of participants within each population of interest have completed the study as the IA data cut time would be very close to the non-inhibitor cohort completions.

b) to move the secondary endpoint of "Total coagulation factor or bypass product consumption" from secondary endpoints to tertiary/exploratory endpoints as there is no uniform unit of measure between factor-replacement products and bypass agent products and in agreement with Paediatric Committee (PDCO), a European Medicines Agency scientific committee.

c) to remove "Percentage of participants with no treated bleeding episodes" from secondary endpoints. This will be presented as part of descriptive analysis for the primary endpoint (ie, ABR of treated bleeding episodes), following agreement reached with FDA.

d) to incorporate the recently issued global Protocol Administrative Change Letter (PACL) dated 31 January 2022, issued primarily to reintroduce the collection of hematology and serum chemistry samples from adolescents at Visit 20/Study Completion. The collection of dilute prothrombin time samples at Visit 20/Study Completion from adolescent participants

is removed in this amendment, to offset the additional blood volume required by reintroducing the collection of hematology and serum chemistry at the same study visit. These changes were made in response to the interaction with a country Health Authority.

e) to include a change in local regulation for the informed consent requirements in Japan, where participants usually considered adults when reaching the age of 20 years, will be considered adults when reaching the age of 18 years instead, as of 01 April 2022. This change is included in the Country-Specific Requirements appendix for Japan.

Section # and Name	**Description of Change**	**Brief Rationale**
Throughout	Revised "drug" to "intervention"	Revised according to updated standard language used in sponsor protocol template.
Section 1.1 Synopsis; Section 3 Objectives, Estimands, and Endpoints	Moved the secondary endpoint of "Total coagulation factor or bypass product consumption" from secondary endpoints to tertiary/exploratory endpoints Removed "Percentage of participants with no treated bleeding episodes" from secondary endpoints. Added Estimands.	This endpoint was moved from Secondary to Tertiary/Exploratory in agreement with Regulatory Authority, as determining equivalent units of measure between factor-replacement products and bypass agents is not feasible.
Section 1.3 Schedule of Activities (SoA), Observational Phase, FVIII or FIX Inhibitor Notes	Removed: At each timepoint, two aliquots will be collected for the central laboratory analysis to measure FVIII or FIX Inhibitor.	Lab sample specifications were removed as these details are provided/maintained in the laboratory manual.
Section 1.3 Schedule of Activities (SoA), Active Treatment Phase, FVIII or FIX Inhibitor / FVIII or FIX activity Notes	Removed: Two aliquots will be collected at each timepoint for central laboratory analysis.	Lab sample specifications were removed as these details are provided/maintained in the laboratory manual.
Section 1.3 Schedule of Activities (SoA), Active Treatment Phase, Hematology and Serum	Removed: **These samples are collected from all adult participants; however, do not collect this sample from any adolescent participants at Visit 20. Removed asterisks from Visit 20.	Included testing for adolescent participants hematology and serum chemistry at this visit according to agreement between sponsor and a country Health Authority.

Section # and Name	Description of Change	Brief Rationale
Chemistry (with lipid profile) Notes		
Section 1.3 Schedule of Activities (SoA), Active Treatment Phase, Biomarkers (TFPI, PF1+2, D-dimer, dPT, TGA) Notes	Added: **These samples are collected from all adult participants; however, **dilute prothrombin time (dPT) will not be collected** from any adolescent participants at Visit 20. Added asterisks from Visit 20.	Removed testing for adolescent participants of dilute prothrombin time at this visit according to agreement between sponsor and a country Health Authority and in order to reduce blood volume collected from adolescent participants.
Section 2.3 Benefit/Risk Assessment, Potential Risks	Revised: Individuals may experience risks or discomforts at the anatomical site of SC injection with PF-06741086. ~~Injection Site Reactions, which may include pain, swelling, bruising, induration, and hematoma, are considered adverse drug reactions for PF-06741086.~~ Injection Site Reactions, which may include bruising, erythema, hemorrhage, hematoma, induration, pain, pruritis, rash, swelling, and warmth are considered adverse drug reactions for PF-06741086. Administration sites of marstacimab by SC injection may include the anterior thigh, backside of upper arm, and abdomen. Participants should rotate injection sites. Other locations are acceptable if required. If an arm is used for the SC injection, the opposite arm should be used for blood sample collections, when needed. Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection dose). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided. Important p~~P~~otential risks for healthy volunteers for treatment with marstacimab ~~PF-06741086~~ are formation/development of thrombi or emboli. Depending on location and severity, thrombi or emboli may be life-threatening or fatal. Non-important potential risks for participants with hemophilia A or B (with or without inhibitors) receiving treatment with marstacimab are formation/development of thrombi or emboli. Depending on location and severity, thrombi or emboli may be life-threatening or fatal. Because PF-06741086 is a fully human IgG1 with no endogenous counterpart, the ADA response is expected	This was revised according to language revisions in updated Investigator's Brochure.

Section # and Name	Description of Change	Brief Rationale
	to primarily affect the PK, efficacy and/or measurement of PF-06741086. An additional potential immunogenicity risk is the ADA-induced hypersensitivity (systemic and localized allergic reactions). ~~Therefore, individuals with a diagnosis or history of thrombotic or ischemic disease (including myocardial infarction, deep venous thrombosis or pulmonary embolism), individuals with coronary artery disease and individuals with an allergy to hamster protein should be excluded from study participation.~~	
Section 2.3.1 Risk Assessment	Added Potential Risk of Clinical Significance Table.	Table included according to new content in sponsor's protocol template.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Removed: ~~Participants in the Inhibitor Cohort must meet the following criteria:~~ ~~• Documentation of current high titer inhibitor (≥5 BU/mL) or current low titer inhibitor (<5 BU/mL).~~ ~~• Participants who have documented inhibitors while on factor replacement therapy but who do not meet the quantitative inhibitor criteria described in the prior bullet at the time of Screening may be considered for eligibility on a case-by-case basis with previously documented approval from the Pfizer medical monitor. Participants with inhibitors qualifying on this basis will be expected to have documented recovery of levels of less than 60% following FVIII or FIX replacement within 6 months of study enrollment.~~	This was removed as it is a description of eligibility requirements at Enrollment/Visit 2 but not a requirement.
Section 6.4 Study Intervention Compliance	Added: The eDiary data must be reviewed at each study visit (ie, at each telephone contact and in-person study visit).	Added to reinforce the need for Diary data review by sites at each scheduled contact with participants, to ensure data accuracy/integrity.
Section 7.1 Discontinuation of Study Intervention	Revised: Criteria for decreasing dosing in an individual participant are as follows: • Moderate severity ~~infusion/~~injection site reactions at more than 2 consecutive ~~visits~~doses of study intervention;	Added editorial changes and a requirement to work directly with sponsor Medical Monitor for participant safety oversight and management of care with COVID-19 infection during Active Treatment Phase of study.

Section # and Name	Description of Change	Brief Rationale
	… The differential diagnosis of COVID-19 is based on the investigator's medical judgement ~~and~~. Confirmation of the diagnosis ideally should be confirmed by a positive SARS-Cov-2 test; however, this test is not required. All participants with confirmed or suspected symptomatic COVID-19 infection should be discussed with the Pfizer Medical Monitor to determine the necessary steps prior to resumption of treatment with study intervention.	
Section 7.2.1 Withdrawal of Consent	Added section: Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol specified follow up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.	Section added according to new content in sponsor's protocol template.
Section 8 Study Assessments and Procedures	Removed blood collection and approximate blood volume table.	Lab sample specifications were removed as these details are provided/maintained in the laboratory manual.
Section 8.1.2 Bleeding	Revised: Bleeding episodes which are related to the participant's hemophilia will not be reported as AEs unless associated with a SAE, although the concomitant events associated with a bleed may be reported as an AE if appropriate (~~eg, a fracture, pain –~~ see Section 8.3.7 for guidance on disease related events [DREs]). …	Editorial change to remove examples in this section, as examples are presented in the referred section.

Section # and Name	Description of Change	Brief Rationale
	Investigators (or designee) ~~or monitors~~ will review the participant's diary/medical records to assist in classification if necessary.	
Section 8.2.5 Injection Site Reaction	Revised: Participants will be ~~provided written instructions and will be~~ trained by the study site staff on the assessment and reporting of injection site reactions. Additionally, the eDiary is programmed to provide reminders to contact the investigator if an injection site reaction occurs.	Editorial changes made as well as clarification that reminder to participants appears in programmed eDiary messaging but not provided to participants in written/printed material.
Section 8.3 Adverse Events and Serious Adverse Events	Updated to align with current protocol template.	Text updated according to new content in sponsor's protocol template.
Section 9.3 Populations for Analyses	Revised mITT description: All participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP).	Included text related to inhibitor participants on routine prophylaxis with bypassing agents as this patient population is now eligible to participate but will only be included in safety analyses (but not efficacy analyses).
Section 9.4.1 Efficacy Analyses	Removed secondary endpoints: •Percentage of participants with no treated bleeding episodes will be analyzed using a McNemar's test to test the null hypothesis that the 2 treatments (PF-06741086 prophylaxis and the on-demand) are equivalent. Treatment effect will be expressed as the difference in percentages. •The Total Factor/bypass product consumption as measured in total IU and IU/kg per month and per year will be analyzed using the Wilcoxon signed rank test (within participant comparison), with treatment effect estimated as the median difference.	Secondary endpoint "Percentage of participants with no treated bleeding episodes…" was removed in agreement with Regulatory Authority and will be presented as part of descriptive analysis for the primary endpoint. Secondary endpoint "The total factor/bypass product consumption…" was removed (and added to "Tertiary/Exploratory Endpoints") as there is no uniform unit of measure between factor-replacement products and bypass agent products and in agreement with PDCO.
Section 9.5 Interim Analysis;	Deleted reference to IA throughout	Previously planned Interim Analysis for futility

Section # and Name	Description of Change	Brief Rationale
Section 10.1.5, Committee Structure	Deleted: ~~Separate interim analyses for futility will be performed for each participant population of interest (Inhibitor Cohort with prior on-demand therapy; Non Inhibitor Cohort with prior on-demand therapy; Non Inhibitor Cohort with prior prophylaxis) when 50% of the planned number of participants either completes or drops off from the ATP. Details of the futility stopping rule will be described in the SAP.~~ … ~~In addition to the ongoing review of the safety data in general, the eDMC will participate in the interim analyses, if performed, to assess efficacy and safety as outlined in~~	removed within each participant populations of interest planned after 50% of participants within each population of interest have completed the study as the Interim Analysis data cut-off time would be very close to the time of completion for other cohorts.
Section 10.3, Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Appendix updated to align with current protocol template.	Text updated according to revised content in sponsor's protocol template.
Section 10.7.1 Japan Appendix	Added: **Section 1.3. Schedule of Activities (SoA)** Active Treatment Phase (ATP); Visit 10; PF-06741086 sample collection For adolescent participants in Japan, this sample (PF-06741086 at Visit 10) will only be collected from adolescent participants with a body weight >40 kg … Revised: Section 10.1.3. Informed Consent Process Additional text added: For Japanese minor participants (under 20 years of age~~,~~ <u>before 31 March 2022, under 18 years of age after 01 April 2022),</u> it is necessary that the participant's parent or a caregiver, etc. sign the informed consent form,	Added to provide country-specific details for Japan, according to adolescent sample volume limitations and according to Japanese regulatory requirements.

Section # and Name	Description of Change	Brief Rationale
	regardless of whether the participant has signed the assent document.	
Sections 10.7.1 Japan Appendix and 10.7.3 China Appendix	Removed blood collection blood volume tables.	Lab sample specifications were removed as these details are provided/maintained in the laboratory manual.
Section 10.7.2 France Appendix	Added: Contrat Unique 1. GCP Training Before enrolling any participants, the investigator and any sub-investigators will complete the Pfizer provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials. 2. Study Intervention No participants or third-party payers will be charged for study intervention. 3. Urgent Safety Measures In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of. 4. Termination Rights Pfizer retains the right to discontinue development of marstacimab at any time.	This was added according to French Regulations and to this language was added to sponsor's updated protocol template.
Section 10.12, Appendix 12 Alternative Study	Revised Text:	Text updated according to revised content in sponsor's protocol

Section # and Name	Description of Change	Brief Rationale
Procedures During ~~COVID-19 Pandemic~~ Public Emergencies	~~In response~~ The alternative study measures described in this section are to be followed during public emergencies, including the ~~global~~ COVID-19 pandemic~~,~~. This appendix applies for the ~~following changes were incorporated into~~ duration of the ~~protocol to clarify alternative solutions to accommodate study procedures.~~ COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer. Use of these ~~COVID-19 temporary~~alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any ~~pertinent~~ quarantines and travel bans/advisories). ~~Notify Pfizer when conditions have returned to business~~ 10.12.1. Home Health Visits A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit as ~~usual. In the event that an in-clinic or unscheduled study visit cannot be conducted after~~of Active Treatment Phase (ATP) Visit 8 (ie, Day ~~-7~~, Visit), study sites are permitted to defer the conduct of the procedures, listed below, to the home health/mobile phlebotomy services or local medical establishments, provided that local regulations permit: … Removed: ~~-Dose Escalation Assessment (starting Visit 14, ATP Day 180).~~ … 10.12.2. Telehealth Visits In the event that in-clinic visits cannot be conducted, every effort should be made to follow- up on the safety of study participants ~~by phone contact. Video contact can~~at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used ~~if permitted by local regulations. During the phone (or~~ to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video~~) contact, the~~ , video-conferencing software) remotely, allowing the	template and to include provisions for public emergencies, in addition to those associated with COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
	participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments ~~should~~must be performed during a telehealth visit: … Study participants must be reminded to promptly notify site staff about any change in their health status. If the participant or caregiver has any concerns regarding his safety and an in-clinic or unscheduled study visit cannot be performed due to public emergencies, including COVID-19 pandemic-related issues, then the participant should visit his primary care physician or local clinic for an evaluation and appropriate medical treatment.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol 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

Short Title: PROPHYLAXIS STUDY OF PF-06741086 IN ADOLESCENT AND ADULT HEMOPHILIA PARTICIPANTS WITH OR WITHOUT INHIBITORS

Regulatory Agency Identification Number(s):

US IND Number:	126734
EudraCT Number:	2018-003660-31
ClinicalTrials.gov ID:	NCT03938792
Protocol Number:	B7841005
Phase:	3

Rationale:
Treatment with PF-06741086 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 are expected to result in a reduction of bleeding episodes.

Objectives, Estimands, and Endpoints

Primary Objectives	Endpoints	Estimands
To demonstrate the efficacy and safety of PF-06741086 for routine prophylaxis in severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%,	<u>Primary Efficacy Endpoint</u> The primary efficacy endpoint is the ABR of treated bleeding events.	<u>Efficacy Estimands</u> <u>Population Summary</u> • Inhibitor Cohort (participants with prior on-demand therapy) for all regions: the population summary will utilize the

respectively) participants 12 to <75 years of age with or without inhibitors	Safety Endpoints Type I error control will not be applied to the following safety endpoints: • AEs and SAEs • Incidence and severity of thrombotic events • Incidence and severity of thrombotic microangiopathy • Disseminated intravascular coagulation/consumption coagulopathy • Immunogenicity (incidence of ADA and clinically significant persistent NAb against PF-06741086) • Incidence and severity of injection site reaction • Changes in physical examination and vital signs • Incidence of clinically significant laboratory value abnormalities • Incidence of severe hypersensitivity and anaphylactic reactions	ratio of the mean ABR (marstacimab prophylaxis vs on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. • Non-Inhibitor Cohort for regions outside the EU: the population summary will utilize the ratio of the mean ABR (marstacimab prophylaxis vs on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. • Non-Inhibitor Cohort for the EU: the population summary will utilize the mean ABR difference (marstacimab prophylaxis – prior prophylaxis treatment) based on adult and adolescent participants meeting the entry criteria with prior prophylaxis therapy. Intercurrent Events • For all cohorts and regions, all data collected while receiving rescue medication in the form of factor replacement or bypass therapy are included. However, all data during the preventative treatment for medical/dental

		procedures, sport activity, or physical therapy (plus 72 hours), or collected after dose modification and/or discontinuation of treatment will not be included. Safety Estimands • The safety estimand for AEs/SAEs will consider all safety data collected irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures. Specifically, all data collected on or after obtaining informed consent/assent will be included in the clinical study report. • All other safety assessments will consider a "while on treatment" evaluation irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures.
Secondary Objectives	**Endpoints**	**Estimands**
To evaluate additional efficacy of PF-06741086	For the Non-Inhibitor Cohort, the primary endpoint with respect to comparisons with prior on-demand therapy for regions outside EU will be a secondary endpoint for the EU. Likewise, the primary endpoint with respect to comparisons with prior prophylaxis therapy for the EU	• For incidences of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds, the estimand will utilize the same population summary and intercurrent event handling as in the primary endpoint for each of the

	will be a secondary endpoint for the regions outside EU. The following parameters will be assessed for comparison between PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus a respective control group corresponding to each of the 3 statistical objectives (inhibitors [participants with prior on-demand therapy], non-inhibitors [with prior on-demand therapy], and non-inhibitors [with prior prophylaxis therapy]). • Incidence of joint bleeds • Incidence of spontaneous bleeds • Incidence of target joint bleeds • Incidence of total bleeds (treated and untreated) • Change in joints as measured by the Hemophilia Joint Health Score (HJHS)	following: inhibitor cohort for all regions, non-inhibitor cohort for the regions outside of the EU, and non-inhibitor cohort for the EU. • For HJHS, the difference in mean changes from baseline at 6 months between the marstacimab prophylaxis in ATP versus the respective reference therapy in OP will be presented using the data irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures. Observations after discontinuation of treatment, if collected, will not be included.
To evaluate the effect of PF-06741086 on Health-related quality of life (HRQoL)	HRQoL: • Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) (≥17 years of age)/Hemophilia Quality of Life Questionnaire for Children (Haemo-QoL); (Adolescents 12 to <17 years of age); • Hemophilia Activities List (HAL) (Adult ≥17 years of age)/Pediatric Hemophilia Activities List (pedHAL)	The estimand for all HRQoL endpoints will utilize the same population summary and intercurrent event handling as in the HJHS.

	(Adolescents 12 to <17 years of age); • Patient Global Impression of Change – Hemophilia (PGIC-H) (Observational Phase and Active Treatment Phase) • Health Utilities Measure (EuroQol 5 Dimensions 5 Level [EQ-5D-5L])	
Tertiary/Exploratory Objectives	**Endpoints**	**Estimands**
Assess PK and PD parameters in this study population	• Analysis of PF-06741086 (marstacimab) concentrations (trough as well as post-dose) over the duration of the study • Analysis of changes in biomarkers: TFPI (total and free), PKT, PF1+2, D-dimer, and dilute prothrombin time over duration of the study	Not Applicable
To evaluate the effect of PF-06741086 on Health-related quality of life	• Hemophilia Life Impacts Questionnaire	Not Applicable
To compare joint health post PF-06741086 to baseline	• Number of target joints	Not Applicable
To evaluate the effect of PF-06741086 on total coagulation factor or bypass product consumption	• Total coagulation factor or bypass product consumption	Not Applicable

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 factor VIII [FVIII] activity <1% or factor IX [FIX] activity ≤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]). For simplicity the drug name will be referred to as PF-06741086 throughout the remainder of the document.

Disclosure Statement:
This is a Cross-Over Prevention study with 1 Arm that 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 eg FEIBA or in regions where available, BYCLOT (Inhibitor Cohort) and individuals without inhibitors will receive on-demand treatment with FVIII- or FIX-replacement therapy (Non-Inhibitor 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.

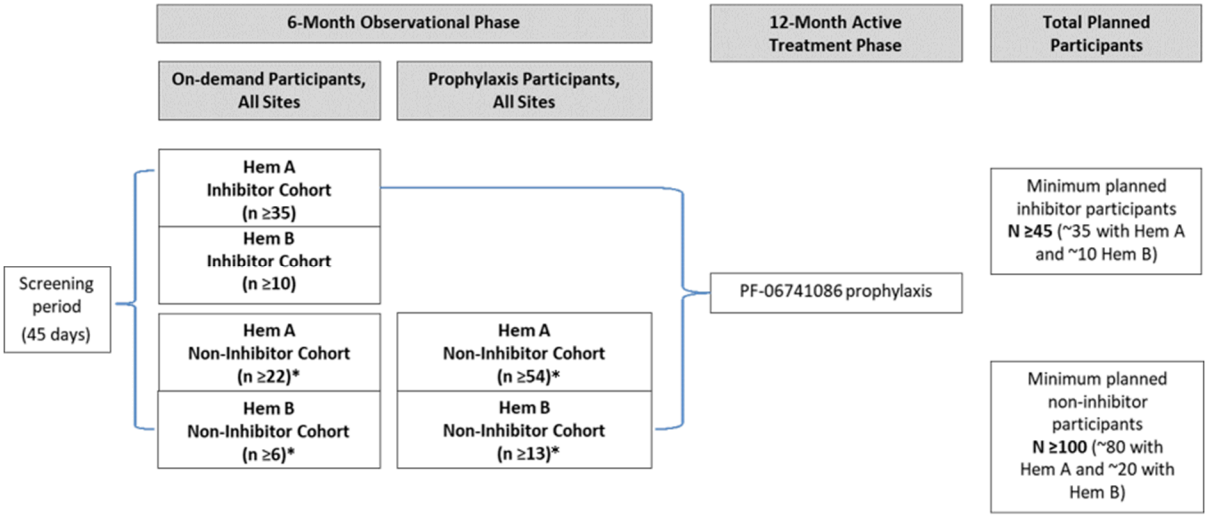
Participants with inhibitors who are on routine prophylaxis (defined as treatment by IV injection of bypass agent to prevent bleeding) may be considered for eligibility on a case-by-case basis at the discretion of the sponsor, following discussion and agreement from the Pfizer medical monitor. These participants will be included in addition to the On-Demand Inhibitor participants and will supplement the safety evaluation of the inhibitor cohorts.

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.

Approximately CCI % of the overall planned enrollment into Study B7841005, which has an anticipated sample size of approximately 145 global participants, will come from China per local registration requirements. Study B7841010 is the ongoing local Chinese PK study that is scheduled to enroll up to 6 participants. These participants will be eligible to roll into the global enrollment pool in Study B7841005, assuming they meet all study entry criteria and global enrollment has not been achieved. In addition, considering that global enrollment into Study B7841005 may be completed prior to enrollment of additional Chinese participants, local participants will also continue to be randomized into a China extension cohort after the study has achieved its global enrollment targets. Local Chinese B7841005 study participants enrolled during global enrollment and in the China extension cohort will be pooled together to form the China cohort and will be analyzed to support the registration in China only. Data analysis of the global trial will not include participants enrolled in the China extension cohort.

1.2. Schema

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.

1.3. Schedule of Activities (SoA)

Alternative study visit information pertaining to the COVID-19 pandemic is described in Appendix 12 (Section 10.12).

	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	
Visit Window	-----	-----	±7 days	-----	
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.

	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	**-----**	
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.

	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	

	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	→	→	→	

Abbreviations: → = ongoing/continuous event; PCC = prothrombin complex concentrates; aPCC = activated prothrombin complex concentrates; cTnI = cardiac troponin I; ECG = electrocardiogram; FIX = factor IX; FVIII = factor VIII; HIV = human immunodeficiency virus; HJHS = Hemophilia Joint Health Score; Patient's Global Impression of Change – Hemophilia (PGIC-H); OP = Observational Phase; rFVIIa = recombinant factor VIIa.

		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. 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).
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	
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		

		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</u> 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).
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.

		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</u> 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).
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	
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**	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</u> 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).
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	
																		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		Participants must be fasting at least 12 hours prior to blood draw for Lipid Profile. *These samples are collected from all adult participants; however, only collect this sample from adolescent participants if their weight is >40 kg at Visit 18.
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**	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</u> 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).
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	
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</u> 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).
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	
Immunogenicity Tests	X				X	X		X				X		X		X		Anti-drug antibodies and neutralizing antibodies to PF-06741086.
Serology Tests	X																	Hepatitis B surface antigen, hepatitis B core antigen antibody, hepatitis C virus antibody, HIV (and CD4 count).

		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</u> 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).
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	
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**	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</u> 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).
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	
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.

		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</u> 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).
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		The Day 0 Pre-Dose results for **Fibrinogen** 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.

		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</u> 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).
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		**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.
ECG		X								X						X		Triplicate ECG 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,

		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</u> 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).
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**	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. 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).
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).

		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. 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).
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	
Study intervention administered by participant/caregiver				X	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**	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</u> 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).
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**	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</u> 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).
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	
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	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	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</u> 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).
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 dispensed or collected. 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**	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</u> 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).
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</u> 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).
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		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.
Concomitant Treatment(s)			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	Includes concomitant medication and non-medication treatments such as surgeries and procedures.
Serious and non-serious adverse event monitoring	X	→		→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Abbreviations: → = ongoing/continuous event; ADA = anti-drug antibody; ATP = Active Treatment Phase; PCC = prothrombin complex concentrates; aPCC = activated prothrombin complex concentrates; aPTT = activated partial thromboplastin time; cTnI = cardiac troponin I; ECG = electrocardiogram; FIX = factor IX; FVIII = factor VIII; HIV = human immunodeficiency virus; HJHS = Hemophilia Joint Health Score; NAb = neutralizing antibody; INR = international normalized ratio; PGIC-H = Patient Global Impression of Change – Hemophilia PT = prothrombin time; rFVIIa = recombinant factor VIIa; TFPI = tissue factor pathway inhibitor.

2. INTRODUCTION

PF-06741086 (generic name: marstacimab) is a human monoclonal immunoglobulin G isotype, subclass 1 (IgG1) that targets the Kunitz 2 domain of tissue factor pathway inhibitor (TFPI). PF-06741086 is in development as a prophylactic treatment to prevent or reduce the frequency of bleeding episodes in individuals with severe hemophilia A or moderately severe to severe hemophilia B (defined as FVIII activity <1% or FIX activity ≤2%, respectively) with or without inhibitor.

2.1. Study Rationale

Treatment with PF-06741086 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 will work in the presence of inhibitors. The potential for QW 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.

2.2. Background

The current standard of care for treatment of individuals with hemophilia A or B is replacement of their deficient clotting factor using FVIII or FIX clotting factor concentrate, respectively.[1] Replacement therapy is administered to treat or prevent acute bleeding episodes, to provide hemostasis during surgery, invasive procedures and the subsequent wound healing period, or to provide routine prophylaxis to prevent bleeding episodes. However, a subset of patients with hemophilia develop neutralizing antibodies (inhibitors) directed against FVIII or FIX, reducing the effectiveness of factor replacement therapy as a first line therapy for prophylaxis against or treatment of hemophilia bleeding episodes.[2] For patients who respond to clotting factor replacement, the IV administration route and frequency of infusion required for effective prophylaxis treatment remains burdensome and may result in reduced adherence and compromised prophylactic efficacy. As well, venous access for IV administration of clotting factor concentrates is limited in the youngest pediatric patients with hemophilia. In these patients, indwelling central venous catheters are frequently required to assure venous access with the attendant infectious and thrombotic complications. Thus, an unmet medical need exists for a stand-alone QW SC intervention to promote hemostasis and coagulation as well as improve treatment compliance in patients with hemophilia in lieu of coagulation factor replacement therapy.

TFPI is a protease inhibitor, which acts as an antagonist of the extrinsic coagulation pathway via inhibition of tissue factor-activated coagulation factor VII (FVIIa) and activated factor X (FXa).[3] TFPI has 2 isoforms, TFPIα and TFPIβ. The 2 isoforms share 2 of the same Kunitz type domains (K1 and K2), but TFPIβ lacks the K3 domain. Isoforms are distributed in plasma and on vascular endothelial cell surfaces through glycosylphosphatidylinositol anchors. TFPIα is also located in platelets. Available data indicate that a reduced quantity of TFPI in plasma is associated with faster coagulation times and increased thrombin generation.[4] Individuals with TFPI free antigen at the 5th percentile and 2nd percentile have an odds ratio for deep vein thrombosis that is 2.1- and 2.2-fold that of the general population,

respectively, indicating a wide therapeutic index is associated with modulation of TFPI activity.[5] Additionally, single doses of PF-06741086 have been evaluated in a Phase 1 FIH study without significant adverse effects. These results suggest that TFPI may serve as an acceptable target for a pharmaceutical treatment to reduce inhibition of the extrinsic coagulation pathway and thereby increase clotting activity in participants with bleeding disorders, such as hemophilia.

PF-06741086 is a fully humanized monoclonal IgG1 that targets the shared K2 domains of TFPIα and TFPIβ. PF-06741086 is administered in a saline solution via IV or SC injections. Nonclinical studies indicate that efficacious concentrations of the antibody can be projected with weekly SC QW injections.

To date, 3 clinical studies with PF-06741086 (Protocols B7841001, B7841002, and B7841003) have been completed.

Study B7841001 was a Phase 1, FIH, single ascending dose study in male healthy participants ages 18 to 55 years with no history of thrombotic events or coronary artery diseases, no demographic or clinical risk factors associated with thrombosis (eg, tobacco use), and no acquired or hereditary pro-thrombotic conditions. PF-06741086 was administered to 32 participants whilst 9 participants received placebo. The doses administered were: 30, 100, and 300 mg SC and 150 and 440 mg IV. All doses administered in this study were well tolerated and there were no SAEs, severe TEAEs, or safety laboratory values of concern for these participants. There were also no reported infusion or injection site reactions following administration of PF-06741086 in study B7841001. The PK parameters could not be characterized after the 30-mg dose administration, but otherwise, the long half-life (33.30 ± 5.39 [mean ± standard deviation] after 100 mg SC to median 98.35 [74.7-122 (minimum – maximum)] hours after 300 mg SC) supports QW administration.

The second completed study, B7841002, was a Phase 1b/2, open-label, multiple ascending dose study in participants with hemophilia A or B. This study was designed to evaluate the safety, tolerability, PK, PD, and efficacy of PF-06741086. Participants in this study were enrolled in 4 cohorts that were planned to receive 300 mg SC QW, 300 mg SC loading dose and 150 mg PF-06741086 SC QW, and 450 mg SC QW respectively. Frequency and route(s) of administration after the first dose may be modified based on review of available data. Twenty-six (26) participants have been treated in this study of multiple ascending dose levels of PF-06741086.

The most common treatment-emergent and treatment-related AEs (reported in at least 2 participants in a respective cohort) were injection site bruising in 2/7 (28.6%) participants in Cohort 1, hypertension in 2/6 (33.3%) participants in Cohort 2, injection site swelling in 2/6 (33.3%) and headache in 2/6 (33.3%) participants in Cohort 3. There have been 5 total SAEs reported, 4 of which are treatment emergent in Study B7841002. There have been no treatment-related SAEs.

A negative binomial model was used to compare the ABR between PF-06741086 dose cohorts and the historical On-Demand group. There was a statistically significant reduction

in ABR in the pooled PF-06741086 dose cohorts (24 participants) versus that in the historical On-Demand group (ratio [test/reference] = 0.10, 80% CI = 0.07 to 0.14, p <0.0001). The reduction in ABR remained statistically significant in each PF-06741086 dose cohort versus that in the historical On-Demand group.

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

Sensitivity analyses were conducted using an exact Wilcoxon-rank sum test. There was a statistically significant difference in ABR between the pooled PF-06741086 dose cohorts and the historical On-Demand group (p <0.0001), and the difference remained statistically significant in each PF-06741086 dose cohort versus that in the historical On-Demand group. There was a statistically significant difference between on-study and pre-treatment ABR in the pooled PF-06741086 dose cohorts (p <0.0001), and the difference remained statistically significant in each PF-06741086 dose cohort.

The results of in vitro and in vivo nonclinical combination pharmacology studies of PF-06741086 and rFVIIa or FEIBA support concomitant use of rFVIIa at a clinical dose of ≤90 μg/kg or FEIBA at the clinical dose of 100 U/kg in the event that a breakthrough bleeding episode occurs in a hemophilia participant with an inhibitor to FVIII or FIX. [6]

Study B7841003 was an open-label, Phase 2, long-term extension study designed to evaluate the long-term (treatment up to 365 days) safety and efficacy of male participants with severe (FVIII or FIX activity <1%) hemophilia A and B with or without inhibitors, ages 18 to <75 years, with ≥6 bleeding episodes during the 6 months prior to treatment with study intervention. An amendment allowed de novo and adolescent (ages ≥12 to <18 years) participants to be enrolled, however, no adolescents were subsequently enrolled. Participants were assigned to a 300-mg loading dose of marstacimab followed by 150 mg once weekly or 300 mg once weekly. Safety parameters included AEs, laboratory assessments, ECGs, and vital signs. Efficacy was assessed using ABRs.

In total, 20 participants were enrolled: 150 mg, n=10 (hem A, n=9; hem B, n=1; with inhibitors, n=2); 300 mg, n=10 (hem A, n=10; with inhibitors, n=5). All received ≥1 marstacimab dose. Within the 300-mg once weekly dose cohorts, 15 AEs (2 treatment-related) were reported in 7 participants (70.0%). Within the 150-mg once weekly cohorts, 24 AEs (1 treatment-related) were reported in 7 participants (70.0%). TEAEs were injection-site reactions (n=2) and hematoma (n=1). No participants discontinued because of AEs. No thrombotic events were reported.

Relative to the pre-treatment period, mean ABR decreased by 92.6% and 84.5% in the 300-mg once weekly and 150-mg once weekly cohorts, respectively.

The efficacy result shown in Study B7841002 for the duration of 3 months was maintained in this long-term study where participants were treated up to 1 year across all dose cohorts—inhibitors and non-inhibitors, 150-mg and 300-mg maintenance doses, and hemophilia A and B.

The results of this study demonstrated that long-term treatment with marstacimab was well tolerated and efficacious in participants with severe hemophilia A and B with or without inhibitors.

2.3. Benefit/Risk Assessment

Potential Benefits

Potential benefits of study participation for participants with hemophilia A or B (with or without inhibitors) include effective prophylaxis with PF-06741086 on a weekly SC dosing schedule that substantially reduces the burden of care associated with prophylactic treatment, eliminates the need for frequent IV infusions, potentially obviates the need for indwelling central venous catheters and reduces or eliminates acute treatment of bleeding episodes with FVIII or FIX (or bypass agents), thereby reducing the antigenic exposure to FVIII or FIX.

Potential Risks

Individuals may experience risks or discomforts at the anatomical site of SC injection with PF-06741086. Injection Site Reactions, which may include bruising, erythema, hemorrhage, hematoma, induration, pain, pruritis, rash, swelling, and warmth are considered adverse drug reactions for PF-06741086. Administration sites of marstacimab by SC injection may include the anterior thigh, backside of upper arm, and abdomen. Participants should rotate injection sites. Other locations are acceptable if required. If an arm is used for the SC injection, the opposite arm should be used for blood sample collections, when needed. Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection dose). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided.

Important potential risks for healthy volunteers for treatment with marstacimab are formation/development of thrombi or emboli. Depending on location and severity, thrombi or emboli may be life-threatening or fatal.

Non-important potential risks for participants with hemophilia A or B (with or without inhibitors) receiving treatment with marstacimab are formation/development of thrombi or emboli. Depending on location and severity, thrombi or emboli may be life-threatening or fatal.

Because PF-06741086 is a fully human IgG1 with no endogenous counterpart, the ADA response is expected to primarily affect the PK, efficacy and/or measurement of PF-06741086. An additional potential immunogenicity risk is the ADA-induced hypersensitivity (systemic and localized allergic reactions).

PF-06741086 is expected to have efficacy outweighing the risks in participants who are eligible for this study but will be varied based on a participant's prior hemostatic therapy. All study participants will share the same potential risks regardless of their prior hemostatic therapy, while participants on prior on-demand treatment will potentially realize a greater benefit due to the anticipated reduction in bleeds.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-06741086 may be found in the IB, which is the SRSD for this study.

An additional risk of clinical trials, including Study B7841005, during the COVID-19 pandemic includes contact with other individuals while at or traveling to clinical trial sites. Appendix 12: Alternative Study Procedures During , provides procedures to mitigate these risks for study participants during the COVID-19 outbreak.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Marstacimab		
Potential risk of injection site reactions, including bruising, erythema, hemorrhage, hematoma, induration, pain, pruritis, rash, swelling, and warmth.	The potential risk is based on AEs reported in the Phase 2 and Phase 3 studies. Injection Site Reaction is listed as an ADR in the IB.	Study participants will be closely monitored for signs and symptoms of injection site reaction.
Potential immunogenicity risk of ADA-induced hypersensitivity.	The study intervention is a protein administered SC and capable of inducing ADA-induced allergic reaction.	Excluding participants with known hypersensitivity to the active compounds or to any ingredients (excipients) contained in the formulations. Study participants will be closely monitored for clinical signs and symptoms of immediate or delayed allergic reactions to marstacimab in clinical studies.
Potential risk of thrombi or emboli.	There is a potential risk of developing thrombi/emboli based on the mechanism of action of marstacimab.	Individuals with known coronary artery disease, venous or arterial thrombosis, or ischemic disease are excluded from the study. Study participants are excluded if there are any hemostatic defects other than hemophilia A or B. Treatment-emergent thrombotic events will be actively monitored to mitigate risk of clinically significant thromboembolic events.
Potential risk of thrombi or emboli with COVID-19 infection while also receiving study intervention.	COVID-19 infection may introduce additional risk of thrombi/emboli to potential risk of thrombi/emboli with study intervention administration.	Treatment with study intervention is suspended for any participant who has presumed or confirmed **symptomatic** COVID-19 infection. Participant's resumption of treatment with study intervention is determined in collaboration between principal investigator and Pfizer medical monitor.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing study procedures at a study or other healthcare facilities.	Use of home health/mobile phlebotomy services or local medical establishments may be utilized in the study to minimize potential exposure of trial participants to SARS-CoV-2, where permitted.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Primary Objectives	Endpoints	Estimands
To demonstrate the efficacy and safety of PF-06741086 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	<u>Primary Efficacy Endpoint</u> The primary efficacy endpoint is the ABR of treated bleeding events. <u>Safety Endpoints</u> Type I error control will not be applied to the following safety endpoints: • AEs and SAEs • Incidence and severity of thrombotic events • Incidence and severity of thrombotic microangiopathy • Disseminated intravascular coagulation/consumption coagulopathy • Immunogenicity (incidence of ADA and clinically significant persistent NAb against PF-06741086) • Incidence and severity of injection site reaction • Changes in physical examination and vital signs • Incidence of clinically significant laboratory value abnormalities	<u>Efficacy Estimands</u> <u>Population Summary</u> • Inhibitor Cohort (participants with prior on-demand therapy) for all regions: the population summary will utilize the ratio of the mean ABR (marstacimab prophylaxis vs on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. • Non-Inhibitor Cohort for regions outside the EU: the population summary will utilize the ratio of the mean ABR (marstacimab prophylaxis vs on-demand treatment) based on adult and adolescent participants meeting the entry criteria with prior on-demand therapy. • Non-Inhibitor Cohort for the EU: the population summary will utilize the mean ABR difference (marstacimab prophylaxis – prior prophylaxis treatment) based on adult and adolescent participants meeting the entry criteria with prior prophylaxis therapy.

	• Incidence of severe hypersensitivity and anaphylactic reactions	<u>Intercurrent Events</u> • For all cohorts and regions, all data collected while receiving rescue medication in the form of factor replacement or bypass therapy are included. However, all data during the preventative treatment for medical/dental procedures, sport activity, or physical therapy (plus 72 hours), or collected after dose modification and/or discontinuation of treatment will not be included. <u>Safety Estimands</u> • The safety estimand for AEs/SAEs will consider all safety data collected irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures. Specifically, all data collected on or after obtaining informed consent/assent will be included in the clinical study report. • All other safety assessments will consider a "while on treatment" evaluation irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures.

Secondary Objectives	Endpoints	Estimands
To evaluate additional efficacy of PF-06741086	For the Non-Inhibitor Cohort, the primary endpoint with respect to comparisons with prior on-demand therapy for regions outside EU will be a secondary endpoint for the EU. Likewise, the primary endpoint with respect to comparisons with prior prophylaxis therapy for the EU will be a secondary endpoint for the regions outside EU. The following parameters will be assessed for comparison between PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus a respective control group corresponding to each of the 3 statistical objectives (inhibitors [participants with on-demand therapy], non-inhibitors [with prior on-demand therapy], and non-inhibitors [with prior prophylaxis therapy]). • Incidence of joint bleeds • Incidence of spontaneous bleeds • Incidence of target joint bleeds • Incidence of total bleeds (treated and untreated) • Change in joints as measured by the	• For incidences of joint bleeds, spontaneous bleeds, target joint bleeds, and total bleeds, the estimand will utilize the same population summary and intercurrent event handling as in the primary endpoint for each of the following: inhibitor cohort for all regions, non-inhibitor cohort for the regions outside of the EU, and non-inhibitor cohort for the EU. • For HJHS, the difference in mean changes from baseline at 6 months between the marstacimab prophylaxis in ATP versus the respective reference therapy in OP will be presented using the data irrespective of rescue medication use, dose modification, and/or the preventative treatment for medical/dental procedures. Observations after discontinuation of treatment, if collected, will not be included.

	Hemophilia Joint Health Score (HJHS)	
To evaluate the effect of PF-06741086 on Health-related quality of life (HRQoL)	HRQoL: • Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) (≥17 years of age)/Hemophilia Quality of Life Questionnaire for Children (Haemo-QoL); (Adolescents 12 to <17 years of age); • Hemophilia Activities List (HAL) (Adult ≥17 years of age)/Pediatric Hemophilia Activities List (pedHAL) (Adolescents 12 to <17 years of age); • Patient Global Impression of Change – Hemophilia (PGIC-H) (Observational Phase and Active Treatment Phase) • Health Utilities Measure (EuroQol 5 Dimensions 5 Level [EQ-5D-5L])	The estimand for all HRQoL endpoints will utilize the same population summary and intercurrent event handling as in the HJHS.
Tertiary/Exploratory Objectives	**Endpoints**	**Estimands**
Assess PK and PD parameters in this study population	• Analysis of PF-06741086 (marstacimab) concentrations (trough as well as post-dose) over the duration of the study • Analysis of changes in biomarkers: TFPI (total and free), PKT, PF1+2,	Not Applicable

	D-dimer, and dilute prothrombin time over duration of the study	
To evaluate the effect of PF-06741086 on Health-related quality of life	• Hemophilia Life Impacts Questionnaire	Not Applicable
To compare joint health post PF-06741086 to baseline	• Number of target joints	Not Applicable
To evaluate the effect of PF-06741086 on total coagulation factor or bypass product consumption	• Total coagulation factor or bypass product consumption	Not Applicable

4. STUDY DESIGN

4.1. 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 ≤2%, respectively) with or without inhibitors, 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 (see Section 9.2 Sample Size Determination for additional details). 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]). For simplicity the drug name will be referred to as PF-06741086 throughout the remainder of the document.

The dosing regimen is PF-06741086 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, (see Section 6.6) may have the dose increased to 300 mg SC QW.

Participants will be enrolled into 1 of 2 cohorts:

- Inhibitor Cohort – individuals with inhibitors (approximately 45 participants, with approximately 35 hemophilia A and 10 hemophilia B participants).
- Non-Inhibitor Cohort – individuals without inhibitors (approximately 100 participants, with approximately 80 hemophilia A and 20 hemophilia B participants)

The Inhibitor Cohort (n=45) will include at least 5 adolescent participants and the Non-Inhibitor Cohort will include at least 20 adolescent participants.

Note: The sponsor will provide PF-06741086 during the Active Treatment Phase of this study. Other medication for treatment of hemophilia (eg, factor-replacement products; bypassing agents) will not be provided. The expectation is that non-study hemophilia treatment products used by an individual participant will not change during the study. Any proposed changes to non-study hemophilia medication will require discussion and agreement from the Pfizer medical monitor. Participants will need to obtain non-study intervention through usual means.

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

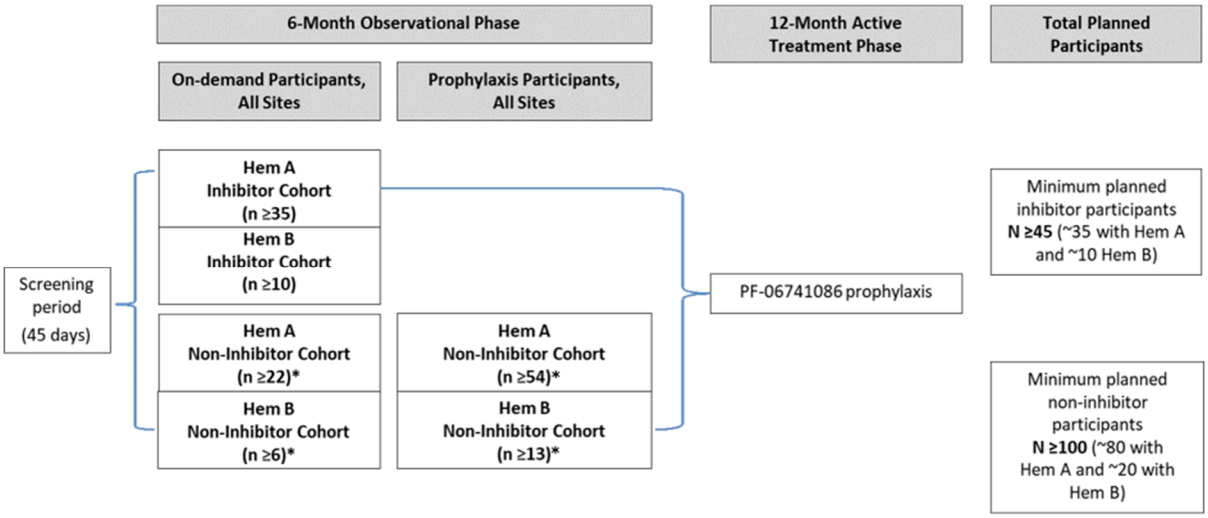
(rFVIIa), Prothrombin Complex Concentrates (PCC), or activated Prothrombin Complex Concentrates (aPCC) agents eg FEIBA or in regions where available, BYCLOT (Inhibitor Cohort) and individuals without inhibitors will receive on-demand treatment with FVIII- or FIX-replacement therapy (Non-Inhibitor Cohort) 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 during the Observational Phase will transition to the Active Treatment Phase after approximately 6 months.

Participants with inhibitors who are on routine prophylaxis (defined as treatment by IV injection of bypass agent to prevent bleeding) may be considered for eligibility on a case-by-case basis at the discretion of the sponsor, following discussion and agreement from the Pfizer medical monitor. These participants will be included in addition to the On-Demand Inhibitor participants and will supplement the safety evaluation of the inhibitor cohorts.

Figure 1 shows the overall study schematic.

Figure 1. 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.

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.

Approximately [redacted] % of the overall planned enrollment into Study B7841005, which has an anticipated sample size of approximately 145 global participants, will come from China per

local registration requirements. Study B7841010 is the ongoing local Chinese PK study that is scheduled to enroll up to 6 participants. These participants will be eligible to roll into the global enrollment pool in Study B7841005, assuming they meet all study entry criteria and global enrollment has not been achieved. In addition, considering that global enrollment into Study B7841005 may be completed prior to enrollment of additional Chinese participants, local participants will also continue to be randomized into a China extension cohort after the study has achieved its global enrollment targets. Local Chinese B7841005 study participants enrolled during global enrollment and in the China extension cohort will be pooled together to form the China cohort and will be analyzed to support the registration in China only (for China country changes refer to Appendix 7: Country-specific Requirements). Data analysis of the global trial will not include participants enrolled in the China extension cohort.

4.2. Scientific Rationale for Study Design

Study B7841005 is being conducted to establish the safety and efficacy of PF-06741086 in male participants 12 to <75 years of age with severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% and FIX activity ≤2%, respectively) with or without inhibitors.

Pfizer believes that it is appropriate to include hemophilia A or B participants in the same study because the mechanism of action of PF-06741086 through the extrinsic cascade predicts it would be effective in both forms of hemophilia. Similarly, it is appropriate to enroll both those with inhibitors and those without, because the mechanism of action would not be influenced by the presences of inhibitors to either FVIII or FIX. Limiting inclusion to only individuals with severe hemophilia A or moderately severe to severe hemophilia B (factor activity level <1% for hemophilia A or ≤2% for hemophilia B) is justified by similar requirements in regulatory guidance for the evaluation of replacement factors for hemophilia A and hemophilia B (European Medicines Agency [EMA] and International Society on Thrombosis and Haemostasis).[7, 8] Similarly, limiting inclusion to only those with at least 6 bleeding or at least 4 bleeding episodes for hemophilia A and B, respectively in the 6 months prior to screening is recommended because these are the participants who would be expected to show therapeutic benefit.

A one-way cross-over design where each participant serves as his own control has been selected as appropriate for this clinical study. This design results in reduced variability between the control and investigation groups through concordance between the control and treatment group. The reduction in variability permits hypothesis testing with a smaller sample size compared to a parallel group design and, within the rare disease indication of hemophilia, has been well-accepted and practiced (B1821002[9] and B1821010[10] studies). As well, emerging regulatory guidance regarding various investigations in this disease area have embraced this approach.[11,12]

The current study also supports sensitivity analyses to address elements that may be perceived to impart bias. While lack of seasonal variation in bleeding rate has been demonstrated by Shafer et al,[13] the current study design permits comparison of the observed bleed rate during the control period (Observational Phase) with the bleed rate observed within the same 6 calendar months during the treatment period (Active Treatment Phase).

The occurrence of any carry over effect from previous treatment (during the Observational Phase) can be assessed in sensitivity analyses by comparing bleed rates during the early part of the treatment period (Active Treatment Phase) with the bleed rate during the latter part of the treatment period (Active Treatment Phase). Furthermore, any carry-over effect from on-demand treatment during the Observational Phase resulting in an increased frequency of bleeding early in the treatment period will impart a conservative bias regarding conclusions of efficacy for PF-06741086 (bias toward higher ABR).

In conclusion, the one-way cross-over design has been selected based on a sample size advantage in this investigation of a rare disease. The current study also allows for the assessment of potential confounding factors via sensitivity analyses.

4.3. Justification for Dose

The doses of PF-06741086 planned for this study are based on the review of the efficacy and safety data from Phase 1/2a studies B7841002 and B7841003.

In a previous study, B7841001, participants were administered single 30, 100, and 300 mg SC and 150 and 440 mg IV doses of PF-06741086. All doses administered in this study were well tolerated and there were no SAEs, severe TEAEs, or safety laboratory values of concern for these participants. There were also no reported infusion or injection site reactions.

Efficacy was demonstrated in study B7841002, where participants received doses of 150 mg (after a 300 mg loading dose) or 300 mg QW. Two dosing regimens, 300 mg SC QW and 150 mg SC QW, with a loading dose of 300 mg SC of PF-06741086 were evaluated as potential Phase 3 doses. Considerations included safety and tolerability, efficacy, PK and PD parameters, immunogenicity, and biopharmaceutics. The 150 mg SC QW with a loading dose of 300 mg SC dosing regimen was selected for Study B7841005. This is largely based on the observed results from Cohorts 1 (300 mg) and 2 (150 mg) in non-inhibitor participants in the ongoing Study B7841002 and supported by the PK/PD modeling results incorporating data from studies B7841002 and B7841001 (FIH in healthy male participants), along with supporting evidence from publicly available information of a number of competitor compounds.

The model-based mean ABR was 4.2, 1.5, 4.2, and 27.6 for the PF-06741086 300 mg SC QW, 150 mg SC QW, 450 mg SC QW, and historical On-Demand control group, respectively. The interim mean ABR for Cohort 4 (300 mg SC QW, inhibitors) was 1. All 3 dosing regimens in Study B7841002 showed statistically significant reduction in ABR (≥85%) compared to the historical On-Demand control group. There was no difference in the ABR observed over 3 months in participants receiving either 150 mg or 300 mg QW. The lower dose of 150 mg QW was chosen because of greater safety multiples and smaller injection volume. Further details are available in the IB for PF-06741086.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the Day 390 Follow-up phone call during the Active Treatment Phase. Participants who will participate in the planned B7841007 long-term extension study are not required to complete the ATP Day 390 Follow-up Phone Call.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

Age:

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

Type of Participant and Disease Characteristics:

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 a 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:

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

   (OR)

   - Participants with on-demand treatment regimen with ≥6 acute bleeding episodes (spontaneous or traumatic) that required coagulation factor infusion during the 6 months period prior to Enrollment into Observational Phase and willing to continue to receive on-demand treatment during the Observational Phase. Surgical bleeding episodes do not apply to this criterion.

4. Participants who are enrolled into the **Inhibitor Cohort** must also meet the following criteria:

   - Documentation of current high titer inhibitor (≥5 BU/mL); or current low titer inhibitor (<5 BU/mL) refractory to FVIII or FIX replacement and with FVIII or FIX

recovery <60% of expected within previous 6 months prior to Enrollment into Observational Phase.

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

Sex:

5. Male

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Previous or current treatment for or history of coronary artery diseases, venous or arterial thrombosis (Common Terminology Criteria for Adverse Events [CTCAE][14] Grade >1), or ischemic disease (except for catheter-associated thrombosis).

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 × upper limit of normal (ULN)

b. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
c. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C -eg, presence of hepatitis B surface antigen [HBsAg] or positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention) is acceptable if the participant otherwise meets entry criteria
d. Serum albumin less than the lower limit of normal (LLN).
e. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2.

5. Abnormal hematology values as defined by the following laboratory tests at Screening:

   a. Platelet count <100,000/uL
   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.

7. QTcF >450 msec for male participants or QTcF >480 msec in participants with bundle branch block.

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

Prior/Concomitant Therapy:

9. Current routine prophylaxis with bypassing agent (eg, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), non-coagulation non-factor replacement therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of 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 non-factor-based hemophilia therapy (eg, fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor.

10. Regular, concomitant therapy with immunomodulatory drugs (eg, IV immunoglobulin [IVIG], and routine systemic corticosteroids, rituximab).

11. Ongoing or planned use of immune tolerance induction during the Observational Phase or Active Treatment Phase, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the Active Treatment Phase.

Prior/Concurrent Clinical Study Experience:

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 PF-06741086 during to participation in Studies B7841002 and B7841003.

Diagnostic Assessments:

14. CD4 cell count ≤200/uL 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.

Other Exclusion Criteria:

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

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should not be assigned the same participant number as for the initial screening.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. When necessary, the site staff may administer study intervention to the participant. The initial 300 mg loading dose will be documented on the CRF. This will not be duplicated in the participant's diary. All other scheduled doses will be recorded on the participant's diary.

6.1. Study Intervention(s) Administered

Arm Name	active study intervention
Intervention Name	PF-06741086 (marstacimab)
Type	Biological product
Dosage Form	Injectable
Dose Strength	150 mg/mL
Dosage	300 mg loading dose then 150 mg QW 300 mg QW[a]
Route of Administration	Subcutaneous injection[b]
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labeling	Study Intervention will be provided in a sterile liquid solution for injection packaged in a prefilled syringe for single use. Each package will be labeled as required per country requirement.

a. 300 mg QW is prescribed for any participant who meets dose escalation criteria (see Section 6.6).
b. Administration of PF-06741086 by SC injection to the anterior thigh, backside of upper arm, and abdomen. Participants should rotate injection sites. If an arm is used for the SC injection, the opposite arm should be used for the PK/PD blood sample collections, if possible. Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection dose). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided.

6.1.1. Medical Devices

1. The manufactured medical devices provided for use in this study is a prefilled syringe, filled with PF-06741086.

2. Instructions for medical device use are provided in the IP manual.

3. All medical device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

4. Further guidance and information for the final disposition of unused study interventions are provided in the Investigational Product Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

For any participant who does not have a qualifying FVIII or FIX Activity laboratory report from a clinical laboratory prior to Screening, a FVIII or FIX Activity sample will be collected prior to Enrollment and after sufficient washout has been completed. In these cases, a washout from current hemophilia product will be required prior to collection of factor activity on Day 1 (in the Observational Phase), as follows:

- from FVIII replacement therapy for at least 72 hours,
- from extended half-life FVIII replacement therapy for at least 4 half-lives
- from FIX replacement therapy for at least 96 hours,
- from extended half-life FIX replacement therapy for at least 4 half-lives,
- from bypass agent therapy from either rFVIIa, PCC, aPCC, or BYCLOT for at least 72 hours.

All participants must meet the following criteria prior to dosing with study intervention in the Active Treatment Phase:

- Prior to dosing, confirmed fibrinogen level ≥LLN.
- Prior to dosing, confirmed prothrombin time (PT) ≤1.25 × ULN.
- Participants remained on same treatment regimen throughout the Observational Phase.

Note: Participants who are prescribed a prophylaxis treatment regimen are permitted to administer prescribed on-demand treatment of bleeding episodes as needed, however, their routine prophylaxis treatment regimen should remain stable during the Observational Phase (eg, participants prescribed "prophylaxis 2 times per week" may not significantly change [at the discretion of the investigator and the sponsor's medical monitor] to a different dose, dosing frequency, or product for prophylaxis treatments during the Observational Phase). Participants who require significant increase in dose or dosing frequency will be withdrawn from the study, at the discretion of the investigator and the sponsor's medical monitor. Participants may receive preventative treatments with their prescribed hemostatic medication prior to planned activity where preventative treatment is prescribed (eg, sport activity or physical therapy). In the event a participant requires preventative treatment prior to surgery or other medical procedure, the investigator should discuss with the medical monitor and agree on planned treatment plan.

The expectation is that non-study hemophilia treatment products used by an individual participant will not change during the study. Any proposed changes to non-study hemophilia medication will require discussion and agreement from the Pfizer medical monitor in order for the participant to initiate dosing with study intervention.

Participants were at least 80% compliant with prescribed treatment regimen during the Observational Phase.

Additionally, participants in the Non-Inhibitor Cohort must meet the following criteria: No detectable or documented history of inhibitors (≥0.6 BU/mL or greater than the ULN for the testing laboratory) against FVIII or FIX during the Observational Phase, and through the Day -7 Visit in the Active Treatment Phase.

If the above protocol-specified criteria are met, participants are eligible to transition into the Active Treatment Phase. If an inhibitor laboratory result obtained from the ATP Visit 6 assessment is received after dosing with study intervention during Visit 7, the participant may continue participation in the ATP of the study based on the medical judgment of the investigator, following discussion with the medical monitor. All other participants who no longer meet the criteria for the cohort to which they are assigned at Baseline (Visit 2) during the Observational Phase will be discontinued from the study.

6.4. 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. The eDiary data must be reviewed at each study visit (ie, at each telephone contact and in-person study visit). Deviation(s) from the prescribed dosage regimen should be recorded. Note: in the event the eDiary is not available, a paper diary may be used during the study.

Study intervention will be administered once weekly. During the Active Treatment Phase, if a participant misses a scheduled dose, the participant should self-administer the missed dose as soon as it has been identified and it may be administered as late as the day prior to next scheduled dose (ie, 6 days later than scheduled for that dosing week). The participant may self-administer the next dose as originally scheduled. If the participant is unable to continue administering the doses as originally scheduled, then the participant is permitted to update the day of dosing for all subsequent doses. Any changes will be documented in the eDiary.

Participants who miss the 150 mg dose during any week during the Active Treatment Phase will need to initially administer a 300 mg loading dose when dosing resumes, and then resume their prescribed dosing regimen (150 mg once weekly). Participants who previously met the protocol specified dose escalation criteria and are administered 300 mg once weekly are already receiving the equivalent of the loading dose via their once weekly dose. When l loading dose is required it is the only dose given on the dosing day. In such cases, the participant's usual once weekly dose will resume the week following loading dose.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, or herbal supplements) that the participant is receiving at the time of Screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy. If a participant has a severe infection, defined as a need for IV antibiotics and has positive culture results available, continued participation of the participant and need for administration of IV antibiotics should be discussed with medical monitor.

In case a participant is scheduled to undergo a surgical procedure, the investigator should contact the medical monitor and discuss further participation for the participant, as well as any other action which may be required.

6.5.1. Permitted Hemostatic Medication

Hemostatic medication allowed for use during the study is presented in Table 1.

Table 1. Permitted Hemostatic Medication

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

Table 1. Permitted Hemostatic Medication

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

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

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

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

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

6.5.2. Prohibited Medications

6.5.2.1. Observation and Active Treatment Phases

The following are prohibited throughout all phases of the study: immunomodulatory medications (eg, IVIG, routine systemic corticosteroids, rituximab) and emicizumab. Bypassing agent therapy is not permitted at any time for the Non-Inhibitor Cohort.

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

6.5.2.2. Active Treatment Phase

The following therapies are prohibited during the Active Treatment Phase unless required for the emergency management of acute breakthrough bleeds in the opinion of the investigator or treating physician. See Section 6.5.3 for further details.

- Non-Inhibitor Cohort: Prophylaxis treatment with FVIII- or FIX-replacement, or any use of bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).
    - Prophylaxis treatments with regularly prescribed hemostatic medication are permitted until initiation of treatment with study intervention at Visit 7.

- Inhibitor Cohort: Prophylaxis, on-demand, or preventative treatment with FVIII- or FIX-replacement. Prophylaxis treatment with bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).

    - When agreed between investigator and Pfizer medical monitor, current routine prophylaxis with bypassing agent are permitted until initiation of treatment with study intervention at Visit 7.

6.5.3. Treatment of Breakthrough Bleeding

If a participant experiences an acute bleeding episode at any point throughout the study, the participant is to be stabilized. A non-inhibitor participant should be stabilized utilizing the participant's standard hemostatic treatment regimen, which may include FVIII- or FIX-replacement therapy. An inhibitor participant should be stabilized utilizing rFVIIa bypass agent therapy or PCC, aPCC, FEIBA, as follows:

- For **non-inhibitor participants** who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or treating physician requires additional hemostatic therapy beyond PF-06741086 prophylaxis, FVIII- or FIX-replacement products may be administered at the lowest effective dose and according to the approved product labeling.

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

    - FEIBA may be administered at the lowest effective dose, in accordance with the Product Prescribing Information but should not exceed 100 units per kg per 24 hours.

    - PCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information.

    - aPCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information.

    - rFVIIa may be administered at the lowest effective dose but not to exceed 90 µg/kg per dose and not to exceed a dosing frequency of approximately every 2 hours *(for Japan country changes refer to Appendix 7: Country-specific requirements).*

        - If a participant receives treatment with rFVIIa at a dose >90 µg/kg or is receiving treatment with rFVIIa more frequently than approximately every 2 hours, the investigator must immediately contact the sponsor's medical monitor to discuss the case. A

determination will be made at that time if the participant should continue to receive PF-06741086, remain in the study, or be withdrawn from further participation.

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

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

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

In instances where a participant is treated for an emergent bleeding event by a non-delegated physician, the investigator and sponsor's medical monitor will discuss and determine the appropriateness of the participant's further participation in the study.

The use of hemostatic medications for breakthrough bleeding as specifically outlined in this Section 6.5.3 is not considered to be a protocol violation.

6.6. Dose Modification

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

Following 6 months of active treatment with PF-06741086, and at any time after completion of Visit 14 (Active Treatment Phase Day 180), the dose may be escalated from 150 mg SC

QW to 300 mg SC QW if the following criterion is met and following discussion with the medical monitor:

- The participant must weigh at least 50 kg in order to escalate to the 300 mg SC QW dose. Any participant weighing between 35 kg and <50 kg, including adolescents, must remain on the 150 mg dose.

- **Non-Inhibitor Cohort:** Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of coagulation FVIII or FIX over a 6-month period in the absence of a confirmed FVIII or FIX inhibitor, respectively.

- **Inhibitor Cohort:** Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of Novo seven FEIBA or in regions where available, BYCLOT over a 6-month period.

Significant spontaneous bleeds are defined as those that lead to a transient or persistent loss of function.[15] The loss of function may be transient and may evidence itself by a reluctance of the participant to utilize the affected body part in usual activities be it on account of pain, associated swelling or limitation in motion. This specification is intended to prevent regimen escalation based upon clinically insignificant or minor bleeding episodes (eg, ecchymoses, epistaxis).

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

6.7. Intervention After the End of the Study

Study intervention will not be provided after conclusion of this study. An extension study (B7841007) to assess safety is available for participants who complete the B7841005 study. Participants who will participate in the B7841007 long-term extension study are not required to complete the Active Treatment Phase Day 390 Follow-up Phone Call.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (ie, study treatment). If study intervention is permanently discontinued, the participant will complete the Study Completion/Termination and Follow-Up Phone Call Visits. Participants not continuing on PF-06741086 following completion or premature discontinuation from this study will be eligible to resume their pre-study factor-based hemostatic products or bypassing agent therapy immediately upon discontinuation of study intervention and while PF-06741086 concentrations are washing out. This approach is justified based on the safe and effective co-administration of PF-06741086 and factor or bypassing agents observed in the development program to date. Participants should not receive emicizumab or any investigational hemostatic products for at least 30 days after receiving the last dose of study intervention during participation in this study.

Note that suspension of study treatment does not represent withdrawal from the study and additional study visits may be completed at the discretion of the investigator or Pfizer medical monitor.

Individual Level Stopping and Dose Adjustment Rules:

Permanent Discontinuation

Active dosing with PF-06741086 will be permanently discontinued in any participant who experiences a TEAE of a Grade 4[14] severity, regardless of presumed relatedness to the study intervention, unless the event can clearly be determined to be unrelated to the study intervention, and will be followed for AE monitoring until resolution or stabilization of the respective toxicity and elimination of study intervention or the end of the study (Day 360), whichever occurs first.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Appendix 5 or if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed.

Interruption or Dose Modification

Active dosing with PF-06741086 will be suspended for any treatment emergent thrombotic event of ≥Grade 3[14] severity, regardless of presumed relatedness to the study intervention, unless the event can clearly be determined to be unrelated to the study intervention. Vessel occlusion related to the insertion or presence of a central venous catheter may be excluded

from this criterion after review of the AE with the respective investigator and the eDMC to assess the event. Following review of the event circumstances and resolution of the AE, dosing may resume if deemed appropriate by the investigator and the sponsor's medical monitor.

Participants who have not experienced TEAE of Grade 4[14] severity, regardless of presumed relatedness to the study intervention, unless the event can clearly be determined to be unrelated to the study intervention, may also require dose modifications in the event that they had been previously increased to the higher 300 mg SC QW dose of PF-06741086 per the protocol (see Section 6.6). Criteria for decreasing dosing in an individual participant are as follows:

- Moderate severity injection site reactions at more than 2 consecutive doses of study intervention;

TEAE(s) that increases in severity/grade, without resolution, (eg, mild to moderate and continuing) after repeat administration of PF-06741086 depending on the sponsor's medical monitor and investigator's evaluation of relationship to PF-06741086;

Any participant who meets the above criteria during treatment with PF-06741086 will be removed from the current dose level to 150 mg SC QW if they are actively receiving 300 mg SC QW or discontinued if they are actively receiving 150 mg SC QW unless the event(s) are incontrovertibly due to extraneous causes or are incontrovertibly complications of hemophilia (see Section 8.3.7 for qualifying events).

Treatment with PF-06741086 will be suspended for any participant who has entered the Active Treatment Phase and has presumed or confirmed, **symptomatic** COVID-19, regardless of severity grade of the associated AE. The differential diagnosis of COVID-19 is based on the investigator's medical judgement. Confirmation of the diagnosis ideally should be confirmed by a positive SARS-Cov-2 test; however, this test is not required. All participants with confirmed or suspected **symptomatic** COVID-19 infection should be discussed with the Pfizer Medical Monitor to determine the necessary steps prior to resumption of treatment with study intervention.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Study Level Stopping Rule:

The study will be stopped following the occurrence of 6 participants experiencing any treatment emergent event of ≥Grade 4[14] severity, regardless of presumed relatedness to the study intervention, excepting those events that can clearly be determined to be unrelated to the study intervention. Based on a study final N of 145 participants in Study B7841005, the

aforenoted rule would be associated with a frequency of 4.1% of participants and the lower bound of the 95% CI around this point estimate would be 1.53%, which exceeds the upper boundary of the 95% CI around the observed rate of life-threatening (CTCAE ≥Grade 4[14]) TEAEs in a hemophilia population that is largely reflective of that to be included in Study B7841005.[1618]

At earlier points in the conduct of the study, this rule will be triggered as follows: 3 participants with events in ≤46 participants treated; 4 participants with events in ≤81 participants treated; and 5 participants with events in ≤121 participants treated.

Additionally, the eDMC will be reviewing safety on an ongoing basis including review of each SAE as it occurs and may make a recommendation, based upon their review of safety and efficacy data, to stop continued prophylactic treatment with PF-06741086 in this study, prior to the stated study level stopping rule being triggered.

Stopping the study will constitute discontinuation of any additional dosing of participants already in the study and cessation of enrollment of new participants. Following review by the eDMC, sponsor, and with agreement from health authorities, as appropriate, resumption of treatment with PF-06741086 may occur.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant experiences symptoms of anaphylaxis or severe hypersensitivity, or newly-occurring inhibitors against FVIII or FIX.

The investigator or sponsor determines that any medical condition may jeopardize the participant's safety if he continues in the study.

The investigator or sponsor determines it is in the best interest of the participant.

A participant may withdraw from the study at any time at his own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- A child's dissent should be respected.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA OP Visit 5 and ATP Day 360 (Visit 20) for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he may request destruction of any remaining samples but data already generated from the samples will continue to be available, and may be used to, to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the clinical trial (CT) SAE Report.

Participants or caregiver may be contacted after completion of the study in order to clarify any data discrepancies or missing data from the period of study participation.

Participants who require a substantial change in their prophylaxis dose or dosing frequency of prior hemostatic agent during the Observational Phase will be withdrawn from the study. Participants withdrawn for this reason may be screened and enrolled at a subsequent date, once the investigator determines the prophylaxis dosing regimen will not be changed.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent/assent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the

withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum planned amount of blood collected from each adult participant at sites in North America, South America, and the EU over the duration of the study should not exceed approximately 349 mL for adult participants with hemophilia A, 328 mL for adult participants with hemophilia B, and the maximum planned amount of blood collected from each adolescent participant in North America, South America, and the EU over the duration of the study should not exceed approximately 245 mL (based on Screening through Active Treatment Phase Visit 20). The maximum planned amount of blood collected from each adult participant at sites in Korea, Hong Kong, Taiwan, and India over the duration of the study should not exceed approximately 354 mL for adult participants with hemophilia A, 333 mL for adult participants with hemophilia B, and the maximum planned amount of blood collected from each adolescent participant in Korea, Hong Kong, Taiwan, and India over the duration of the study should not exceed approximately 251 mL (based on Screening through Active Treatment Phase Visit 20). The total blood volumes over the duration of the study are estimated based on the sample volumes in the laboratory manual. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken from adult participants during the study does not exceed 550 mL during any period of 30 consecutive days. Total blood volume taken from adolescent participants must comply with EMA Guidance entitled, "Ethical considerations for clinical trials on medicinal products conducted with minors."[19] For Japan-specific blood collection and volumes, please refer to Appendix 7 (Section 10.7.1, Japan Appendix). For China-specific blood collection and volumes, please refer to Appendix 7 (Section 10.7.3, China Appendix).

Estimated total blood volume and maximum allowed blood volume collection from the adolescent participant population in this study is based on EMA Guidance entitled, "Ethical considerations for clinical trials on medicinal products conducted with minors."[19] These guidelines direct that total blood volume is estimated as approximately 80 mL/kg – 90 mL/kg. In this study, approximately 90 mL/kg is used as the estimated blood volume for adolescent participants. General criteria (from EMA) for safe blood volume collection in adolescent participants suggests limiting blood draws during a 24-hour period to 1% of total estimated blood volume and limiting blood draws during a 4-week period to 3% of total estimated blood volume. The blood volumes collected from adolescent participants during their participation in this study comply with this EMA Guideline. Where possible, adolescent participant samples should be collected using microtainer devices. Best practices for pediatric blood collection are included in Appendix 2: Clinical Laboratory Tests.

Data to be recorded on the eDiary, on a handheld provisioned device by the participant or caregiver, include weekly injections of PF-06741086 and, when occurring, hemophilic bleeding episodes, including any exogenous factor replacement or bypass therapy that was required to treat the bleeds. The eDiary is programmed to provide reminders for the weekly injections of PF-06741086 and also to contact the investigator if an injection site reaction

(Section 8.2.5) occurs. Note: in the event the eDiary is not available, a paper diary may be used during the study.

8.1. Efficacy Assessments

8.1.1. Hemophilic Bleeding Episodes

During this study, the investigator (or qualified designee) will review the participant diary with the participant, and inquire about and record AEs, concomitant therapy, bleeding episodes (including location and etiology – traumatic or spontaneous), and any hemostatic treatments (including IV treatments with coagulation factor products or bypass agents). Hemostatic therapy that is administered to treat bleeding episodes during the Screening period and during the Observational and Active Treatment Phases through the final study visit will be documented as concomitant therapy. Participant diary review will include any bleeding episodes experienced during participation in this study. Bleeding episodes requiring treatment with IV coagulation factor products or bypass agents will count toward the determination of bleeding episode frequency for the primary efficacy endpoint. Data on the participant diary will be reviewed by the investigator at study visits. Any eDiary noncompliance will be reported to the sponsor. Note: in the event the eDiary is not available, a paper diary may be used during the study.

8.1.2. Bleeding

Occurrences of bleeding episodes will be obtained from participant diaries and medical records. Where relevant, investigators (or qualified designee) and monitors will ensure that there is consistency between the participant's medical record or participant diaries and the AE CRFs, as applicable. Bleeding episodes which are related to the participant's hemophilia will not be reported as AEs unless associated with a SAE, although the concomitant events associated with a bleed may be reported as an AE if appropriate (see Section 8.3.7 for guidance on DREs). Both spontaneous bleeding episodes and traumatic bleeding episodes will be collected. Only bleeding episodes considered not related to the participant's hemophilia, or if the bleeding episodes are considered serious and meet the SAE criteria should be listed on the AE CRF page. When bleeding episodes that meet the SAE criteria are recorded on the AE CRF, the location (site) of the bleed and the etiologic classification as spontaneous or traumatic should be included (as described in Section 8.1.3). The participant diary or medical record will serve as the source document for bleeding episodes during the study. Investigators (or designee) will review the participant's diary/medical records to assist in classification if necessary.

8.1.3. Types of Bleeding

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

Spontaneous Bleeding Episodes: Bleeding episodes should be classified as spontaneous if a participant records a bleeding event when there is no known contributing factor such as definite trauma, antecedent "strenuous" activity, or "overuse". The determination of "strenuous" or "overuse" is at the discretion of the participant/caregiver/investigator. For

example, if a participant were to wake up in the morning and note he was bleeding, a "spontaneous" bleed would be recorded. Target joints can have spontaneous bleeding episodes.

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

8.1.4. Location of Bleeds

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

Note: Until the eDiary is available, a paper diary may be used during the study.

8.1.5. Treatment of Bleeding Episodes

Bleeding episodes that occur during this study may be treated (on-demand) with hemostatic therapy (eg, IV coagulation factor products or rFVIIa bypass agent therapy at approximately 90 μg/kg) as deemed appropriate by the investigator. The specific treatment with hemostatic therapy is at the discretion of the participant/caregiver/investigator, but all doses of hemostatic therapy taken after signing of informed consent will be documented as concomitant medications or concomitant therapy (see Section 6.5.3).

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

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

8.1.6. Hemophilia Joint Health Score (HJHS)

Joint assessments will be performed using the Hemophilia Joint Health Score (HJHS) 2.1 during the Observational Phase, in order to establish a baseline assessment for later

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

8.1.7. Patient-Reported Outcomes

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

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

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

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

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

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

8.1.7.1. ePRO System (PRO and eDiary) Training and Use

Training materials and user guides will be provided to the study site staff and the participants. Before being allowed to enter clinical data into the eDiary or tablet devices, each user must be trained in use of the system and their responsibilities for data entry. Each participant allowed to enter participant data must select a Personal Identification Number

(PIN) that must be kept private. Data will not be able to be entered without first entering the unique PIN or password. The system will authenticate the identity of the user. All users must be trained that passwords and PIN codes are not to be shared. The study site will allow access to view data on the ePRO System to authorized regulatory personnel or sponsor auditors to the extent possible and in conformance with information in the investigator Initiation Package.

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

8.1.7.2. Site Responsibilities for ePRO System

The details of site responsibilities and procedures for the ePRO System will be covered in detail in training material and an instruction manual provided to the study site staff.

The investigator must make sure that the delegation of responsibility to study site staff for administering the ePRO System and training on the use of this system are specifically documented using the appropriate forms and are based on documented evidence of adequate training in administration and use of the ePRO system. Regardless of how the investigator delegates responsibility for administering the ePRO System, the investigator remains responsible for providing adequate supervision and oversight of the colleagues, employees, and any third parties per Food and Drug Administration (FDA) regulations, guidelines, Good Clinical Practice (GCP), and applicable regulations/guidelines of any participating country.

The details of Site Monitor responsibilities and procedures for the ePRO System will be covered in more detail in the Study Monitoring Plan.

8.1.7.3. ePRO System Vendor Responsibilities

The ePRO System will conform to regulations and regulatory guidance concerning data security.

The ePRO vendor will take responsibility for hosting and administration of their database on behalf of the study sites until the study sites have received and accepted the official archive of the clinical data entered into the ePRO System. Data in the database maintained by the vendor during that period are source data. The vendor will not modify the source data except by signed instruction of the relevant investigator or study site staff member specifically delegated that duty by the investigator consistent with GCP and provisions of the protocol.

8.1.7.4. Patient Reported Outcomes (PROs) Assessments

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

Included in the PRO array of measures are the following:

EuroQoL 5 Dimensions (EQ-5D) 5 Level

Developed by the EuroQoL Group, the EQ-5D is considered the premier measure of health status used in the assessment of the Quality Adjusted Life Year. It measures 5 dimensions of health on a 5-point (5L) scale including Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Also included is a visual analog scale anchored by worst and best imaginable health on a 0 to 100 scale where participants are asked to indicate where on the scale they rate their current health.

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

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

HAL and pedHAL

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

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

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

The Patient Global Impression of Change - Hemophilia (PGIC-H) is a single item assessment of the participant's overall impression of change in their life with hemophilia during the 2 distinct phases of Study B7841005 (ie, since being enrolled in the study [PGIC-H Observational Phase] and since being infused/injected with PF-06741086 [PGIC-H Active Treatment Phase]). The recall period for the PGIC-H is reflective of the study phase (ie, "since the start of the study" or "since the infusion received as part of this study". The response scale is a 7-point categorical response scale centered around 'no change' with 3 grades of improvement and 3 grades of worsening.

HLIQ (Exploratory)

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

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

A brief physical examination will include, at a minimum, assessments of the general appearance, the respiratory and cardiovascular systems, as well as participant reported symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in a resting position (either seated or supine) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure, respiratory rate, and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Respiratory rate should be measured by observing and counting the respirations of the participant for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, measurement should be done during the 5 minutes of rest and before blood pressure measurement.

No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement of temperature.

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA at each scheduled timepoint (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

For triplicate ECGs, 3 individual ECG tracings should be obtained approximately 2 to 4 minutes apart.

A Central ECG Reader will provide an interpretation of any abnormal ECGs or any ECGs collected at the time of an abnormal cTnI result.

12-lead ECGs are performed for all participants in a supine position. ECGs will be obtained approximately 2-4 minutes apart; 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.

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 consult with a cardiologist concerning cTnI and 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.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

8.2.4. Clinical Safety Laboratory Assessments

See laboratory manual for the list of clinical laboratory tests to be performed and the SoA for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention must be reported as an AE and should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

cTnI samples will be collected and analyzed only at sites where the local laboratory is equipped to analyze these samples.

8.2.5. Injection Site Reaction

Injection site reactions will be assessed after each dose of PF-06741086 and according to the Schedule of Activities. Study participants will be trained and reminded via the Diary to report all injection site reactions to the investigator or designee. Injection site reactions will be measured using the CTCAE, Version 5.0.[14] These measurements will be categorized by CTCAE Grades 1-5 (Table 2).

Table 2. Common Terminology Criteria for Adverse Events for Injection Site Reactions

Grade 1	Tenderness with or without associated symptoms (eg, warmth, erythema, itching)
Grade 2	Pain, lipodystrophy, edema, phlebitis
Grade 3	Ulceration or necrosis, severe tissue damage, operative intervention indicated
Grade 4	Life-threatening consequences, urgent intervention indicated
Grade 5	Death

If deemed appropriate by the investigator, a consultation with a dermatologist will be performed. Documentation may include a dermatologist report, clinic notes and photographs. Participants will be trained by the study site staff on the assessment and reporting of injection site reactions. Additionally, the eDiary is programmed to provide reminders to contact the investigator if an injection site reaction occurs.

8.2.6. Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine (SCr) concurrent with presence or absence of increase in blood urea nitrogen (BUN) that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr level relative to the participant's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr relative to the participant's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the participant should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Participants should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatine kinase (CK), and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 participants [in a given period/treatment arm] are noted to have 2 consecutive SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

8.3. Adverse Events and Serious Adverse Events, and Other Safety Reporting

The definitions of an AE or SAE can be found in Appendix 3.

The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 6. Device deficiencies are covered in Section 8.3.9.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention/study (see Section 7.1).

During the active collection period as described in Section 8.3.1, each participant/parent/legal guardian/legally authorized representative will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days after the last administration of the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AE or SAE after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3. Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

The investigator should follow the local standard of care to manage the occurrence of a thrombotic event or situations (eg, sepsis and trauma) in which there may be increased

activation of coagulation. Assays for thrombophilic disorders (Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, and protein S level) should only be collected in the event that a participant experiences a thrombotic event at any time during the Active Treatment Phase. All samples collected at the time of a thrombotic event will be analyzed. Refer to Section 7.1 (Discontinuation of Study Intervention) for recommended action with study intervention. Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as

SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Any cardiovascular events and deaths will be assessed on a case-by-case basis through duration of the study.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with hemophilia A or B independent of exposure to study intervention, can be serious/life threatening, and are defined as endpoints in this protocol:

- Bleeding episodes related to hemophilia

Bleeding or bruising, not due to the participant's hemophilia, will be recorded as an AE, and not a DRE.

- Because these events are typically associated with the disease under study, they will not be reported as AEs. These events will be recorded on the Bleed Log page in the participant's eDiary as described in Section 8.1.1 and Section 8.1.2. If the event meets the definition of an SAE, the event will be recorded on the AE CRF page and reported to Pfizer Safety on the CT SAE Report Form within 24 hours or immediately, depending on seriousness criteria met (see Section 8.3.1.1 Reporting SAEs to Pfizer Safety).

8.3.8. Adverse Events of Special Interest

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

AESIs for this study are AEs "injection site reactions" and "thrombotic" events, as well as AEs requiring continuous monitoring (eg, additional laboratory testing) or requiring treatment modification (eg, delay or discontinuation of study intervention). For any participant who develops a thrombotic AE or an AE requiring treatment modifications, please refer to Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal, Individual Level Stopping and Dose Adjustment Rules for conditions under which participants continued administration of study intervention may be discontinued or suspended.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study as a prefilled syringe for the purposes administering study intervention. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix 6.

NOTE: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.3.1 through Section 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Incidents is provided in Appendix 6.

8.3.9.2. Follow-Up of Medical Device Deficiencies

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on a follow-up form with all changes signed and dated by the investigator.

8.3.9.3. Prompt Reporting of Device Deficiencies to the Sponsor

When a device deficiency occurs:

1. The investigator notifies the sponsor by telephone or email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency.
2. The device deficiency must be recorded on the Medical Device Complaint form.
3. If an AE (either serious or non-serious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF.
4. If an SAE associated with the device deficiency is brought to the attention of the investigator, the investigator must immediately notify Pfizer Safety of the SAE (see Section 8.3.1.1). All relevant details related to the role of the device in the event must be included in the CT SAE Report form as outlined in Sections 8.3.1.1 and 8.3.1.2.

The sponsor will be the contact for the receipt of device deficiency information.

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-06741086 greater than 600 mg within a 6 day (144-hour) time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until PF-06741086 can no longer be detected systemically (at least 21 days).

3. Obtain 2 plasma samples (7 days apart) for PK analysis within 7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

5. Overdose is reportable to Safety **only when associated with a SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

If an arm is used for the SC injection, the opposite arm should be used for the PK/PD blood sample collections, if possible.

Blood samples will be collected for measurement of plasma concentrations of PF-06741086 as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the PK samples at designated visits and times as per the SoA. However, as long as the exact date and time of the sample collection is noted on the source document and data collection tool (eg, CRF), the actual time of sample collection will not be captured as a protocol deviation.

Samples will be used to evaluate the PK of PF-06741086. Samples collected for analyses of PF-06741086 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Samples collected for measurement of plasma concentrations of PF-06741086 will be analyzed using a validated analytical method in compliance with applicable standard operating procedures (SOPs).

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample

handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

The shipment address and analytical laboratory contact information will be provided to the investigator site prior to initiation of the study.

PF-06741086 concentration data will be summarized for all participants for each of the study days samples are collected. The data will also be analyzed along with data from other studies using population PK methods. The impact of ADA status will be investigated if there are a sufficient number of participants testing positive for ADA to PF-06741086.

8.6. Pharmacodynamics

Blood samples will be collected for measurement of TFPI (total and free), thrombin generation, PF1+2, D-dimer, and dilute prothrombin time (Section 8.6.1, Section 8.6.2, Section 8.6.3, and Section 8.6.4, respectively). If an arm is used for the SC injection, the opposite arm should be used for the PK/PD blood sample collections, if possible.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. However, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF), the actual date and time of sample collection will not be captured as a protocol deviation.

As part of understanding the PD of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the clinical study report (CSR).

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. These data will be used for internal exploratory purposes and will not be included in the CSR.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the central lab manual.

Biomarker concentration data (TFPI [total and free], thrombin generation, PF1+2, D-dimer, and dilute prothrombin time) will be summarized for all participants for each of the study days samples are collected. The data will also be analyzed along with data from other studies using population PK/PD methods. The impact of ADA status will be investigated if there are a sufficient number of participants testing positive for ADA to PF-06741086.

8.6.1. Tissue Factor Pathway Inhibitor

Blood samples will be collected at each timepoint for TFPI (total and free) analysis as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.6.2. Thrombin Generation Assay

Blood samples will be collected for the thrombin generation assay analysis as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.6.3. Prothrombin Fragment 1 and 2 and D-dimer

Blood samples will be collected for PF1+2 and D-dimer analysis, as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.6.4. Dilute Prothrombin Time

Blood samples will be collected for the dilute prothrombin time analysis as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.7. Genetics

8.7.1. Specified Genetics

Blood samples will be collected for DNA isolation, ONLY at the time a participant experiences a clinically significant AE of thrombosis at any time after initiating dosing with study intervention during the Active Treatment Phase. DNA samples will be analyzed for the purpose of assessing Factor V Leiden mutation and prothrombin 20210 mutation. No other genetic assessments are conducted.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimen collection is not included in this study.

8.8. Biomarkers

The following samples are required and will be collected from all participants in this study as specified in the SoA.

8.8.1. Analysis of Anti-Drug Antibodies and Neutralizing Antibodies to PF-06741086

Blood samples will be collected for determination of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to PF-06741086 as specified in the SoA (see Immunogenicity Tests in ATP) prior to administration of study intervention (at Visit 6). Thereafter, collection of ADA and NAb samples at subsequent visits during the Active Treatment Phase can be collected without regard to relative time from previous dose or next dose with study intervention. Instructions for the collection and handling of biological samples will be provided in the lab manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

Samples collected for determination of ADA and NAb may also be used for additional characterization of the immune response or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.8.2. Specified Gene Expression (RNA) Research

Specified gene expression (RNA) research is not included in this study.

8.8.3. Specified Protein Research

Specified protein research is not included in this study.

8.8.4. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.5. Banked Biospecimens for Biomarkers

Banked biospecimen collection is not included in this study.

8.9. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

This section describes statistical considerations concerning the analysis of "Global cohort". Statistical considerations concerning the analysis of China cohort that will support the registration of China only will be described in the SAP. For details on the Global cohort and China cohort, see Section 4.1.

9.1. Estimands and Statistical Hypotheses

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

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

Participants with inhibitors who are on routine *prophylaxis* (defined as treatment by IV infusion of bypass factor to prevent bleeding) may be allowed to enroll to supplement the safety evaluation of inhibitor cohort. The efficacy of these participants, if included, will be separately summarized using descriptive statistics without any hypothesis testing or inferential statistics.

Non-Inhibitor Cohort

For regions outside of the EU: to demonstrate *superiority* of PF-06741086 prophylaxis observed over a 12-month Active Treatment Phase relative to *on-demand* treatment during the 6 months prior to receiving study intervention, on the ratio of the ABR of treated bleeds using a repeated measures model to account for participant's experience in the OP and ATP, in participants ≥12 years of age with severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) *without* inhibitors who receive *on-demand* treatment during the 6 months prior to receiving study intervention. Superiority will be declared if PF-06741086 prophylaxis reduces the ABR compared to *on-demand* treatment by at least 50%, ie, the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) is below 0.5. Note this is a secondary endpoint for the EU.

For the EU: to demonstrate *non-inferiority* of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase compared to routine *prophylaxis* during 6 months prior to receiving study intervention, on the difference in the ABR of treated bleeds (non-inferiority margin of 2.5) using a repeated measures model to account for participant's experience in the

OP and ATP, in participants ≥12 years of age with severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) *without inhibitors* who receive routine *prophylaxis* treatment during the 6 months prior to receiving study intervention. Non-inferiority will be declared if the two-sided 95% confidence interval of the estimated ABR difference (PF-06741086 prophylaxis – prior prophylaxis) lies below 2.5. If non-inferiority is demonstrated on ABR, subsequent testing for superiority will be conducted on this endpoint. Note this is a secondary endpoint for regions outside the EU.

9.1.1. Estimands

The primary objective is addressed via the primary endpoint of ABR of treated bleeds. For the Inhibitor Cohort (participants with on-demand therapy) for all regions and for the Non-Inhibitor Cohort aiming for regions outside of the EU, the ratio of ABR is estimated for the PF-06741086 prophylaxis for the 12-month Active Treatment Phase during Active Treatment Phase over the on-demand treatment during the Observational Phase. For the Non-Inhibitor Cohort aiming for the EU, the difference in mean ABRs is estimated between the PF-06741086 prophylaxis for the 12-month Active Treatment Phase during Active Treatment Phase and routine *prophylaxis*.

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

With an anticipated trial completion rate of 90%, the derived ABR is expected to closely represent the entire duration of the Observational Phase and the Active Treatment Phase with a minimal rate (<10%) of missing endpoints. Missing values will not be imputed in the primary efficacy analysis. Furthermore, the ABR is derived without regard to the administration of rescue medication use (in the form of coagulation factor replacement or bypass therapy) while any bleeding events after dose increase of PF-06741086 during PF-06741086 prophylaxis (see Section 6.6) are excluded to avoid an inflated efficacy estimate for the 150 mg QW dose of PF-06741086. All data during the preventative medical/dental treatment (plus 72 hours) are also excluded, see Section 6.3. Rescue medication use is assessed directly via a secondary endpoint of total coagulation factor or bypass product consumption.

The method to handle missing data of other endpoints will be discussed in the Statistical Analysis Plan (SAP).

9.2. Sample Size Determination

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

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

For the Inhibitor Cohort (participants with on-demand therapy) in all regions, a sample size of 25 evaluable participants is projected to have ≥90% power (two-sided test with α=0.05) to demonstrate superiority of PF-06741086 prophylaxis in ABR ratio of treated bleeds compared to the on-demand treatment. Superiority will be declared if the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) lies below 0.5 using a repeated negative binomial model with log link function. The assumed mean number of bleeds is in the range of 12.5-15 over the 6 months for on-demand treatment and 4 over the 12 months for PF-06741086 prophylaxis with variances assumed as 6 times mean for both treatments. The correlation between the two bleeding count observations from the same participant was assumed to be 0.2.

For the Non-Inhibitor Cohort for regions outside of the EU, where PF-06741086 prophylaxis is compared with the *on-demand* treatment, the same sample size of 25 evaluable participants will have ≥90% of power to demonstrate superiority of PF-06741086 prophylaxis using the same analysis and the same criterion as in the Inhibitor Cohort.

For the Non-Inhibitor Cohort for the EU where PF-06741086 prophylaxis is compared with routine *prophylaxis*, a sample size of 60 evaluable participants is projected to provide ≥90% power (one-sided test with α=0.025) to show non-inferiority of PF-06741086 prophylaxis compared to routine *prophylaxis* on the difference in ABR of treated bleeds, using a repeated negative binomial model with identity link function, with a non-inferiority margin of 2.5 bleeds/year. For sample size derivation, a simulation was conducted assuming a negative binomial distribution for the mean number of bleeds of 4 over the 12 months for PF-06741086 prophylaxis and 2.5 for routine prophylaxis over the 6 months with variances assumed as 6 times the mean for both treatments. The correlation between the 2 bleeding count observations for the same participant was assumed to be 0.2.

Details regarding the derivation of non-inferiority margin can be found in Appendix 11.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Participant Analysis Set	Description
All Safety	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 non-inhibitor to an inhibitor on or before ATP Day -7 testing will be excluded from this population. Participants who changed from an inhibitor to a non-inhibitor will be included in this population and considered as inhibitors in the analysis. Participants will be analyzed according to the intervention they actually received.
PF-06741086 Safety	All participants who received at least 1 dose of PF-06741086 in ATP.
mITT (modified Intent-to-Treat)	All participants who completed OP and received at least 1 dose of PF-06741086 in ATP (excluding participants with inhibitors who are treated with routine prophylaxis in the OP). Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing will be excluded from mITT; participants who changed from an inhibitor to a non-inhibitor will be included in mITT and considered as inhibitors. This population will be utilized for all efficacy analyses.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints of Global cohort. Analyses for China cohort that will be conducted for registration for China only will be described in the SAP.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Type I error rate for the primary analysis of the primary endpoint will be separately controlled for each statistical objective as two-sided 0.05, or equivalently, one-sided 0.025. The statistical objective and strategy of demonstrating the efficacy in each cohort is shown below. • In all regions, for the Inhibitor Cohort (participants with on-demand therapy), the primary analysis estimates the ABR ratio of PF-06741086 prophylaxis over the on-demand treatment. A repeated measures negative binomial model via generalized estimating equation (GEE) approach with log link is utilized using the number of bleeds requiring treatments as a response variable and treatment (PF-06741086 prophylaxis or on-demand) as a factor. The time in treatment will be an offset variable to account for different follow-up on treatment. Superiority of PF-06741086 prophylaxis is demonstrated if the two-sided 95% CI for the ABR ratio (PF-06741086 prophylaxis/ on-demand) lies below the pre-set threshold of 0.5. The analysis is based on mITT population, and missing values will not be imputed. The bleeding counts in the analysis also include observations during the rescue

Endpoint	Statistical Analysis Methods

	medication use (in the form of coagulation factor replacement or bypass therapy) but excludes observations after dose increase during PF-06741086 prophylaxis (see Section 6.6). All data during the preventative medical/dental treatment (plus 72 hours) is also excluded (see Section 6.3). The ABR of treated bleeds for participants with inhibitors with routine prophylaxis, if included, will be separately summarized using descriptive statistics without any hypothesis testing or inferential statistics.
	• For the Non-Inhibitor Cohort
	  ○ For regions outside of the EU, PF-06741086 prophylaxis is compared with the *on-demand* treatment aiming to show superiority of PF-06741086 prophylaxis using the same analysis method and criterion for declaring superiority as in the Inhibitor Cohort (Note: this is a secondary endpoint for the EU).
	  ○ For the EU, the primary analysis estimates the mean ABR difference between PF-06741086 prophylaxis and the routine *prophylaxis*. A repeated measures negative binomial model via GEE approach with identity link is utilized using the number of bleeds requiring treatment as a response variable and duration and the interaction by treatment (PF-06741086 prophylaxis or routine prophylaxis) and duration as factors without intercept. Non-inferiority is demonstrated if the upper bound of the two-sided 95% CI for the mean ABR difference (PF-06741086 prophylaxis – routine prophylaxis) lies below the pre-set non-inferiority margin of 2.5. If the non-inferiority is established, subsequent testing for superiority may be conducted. The analysis is based on mITT population, and missing values will not be imputed. The bleeding count in the study analysis also includes observations during the rescue medication use (in the form of coagulation factor replacement) but excludes observations after dose increase during PF-06741086 prophylaxis (see Section 6.6). All data during the preventative medical/dental treatment (plus 72 hours) are also excluded (see Section 6.3) (Note: this is a secondary endpoint for regions outside of the EU).
	• Sensitivity analyses and the subgroup analyses/summaries will be described in SAP.

Secondary	For the Non-Inhibitor Cohort, the primary endpoint with respect to comparisons with prior on-demand therapy for regions outside EU will be a secondary endpoint for the EU. Likewise, the primary endpoint with respect to comparisons with prior prophylaxis therapy for the EU will be a secondary endpoint for the regions outside EU. The same statistical analysis methods will be used in the Inhibitor Cohort (participants with on-demand therapy) and the Non-Inhibitor Cohort (participants with on-demand therapy). The analysis methods may differ for the Non-Inhibitor (participants with routine prophylaxis) as described below. Secondary endpoints used for labeling and those that are solely for scientific interest will be specified in the SAP. The method used for controlling the type I error rate within each statistical objective will also be described in the SAP. Inhibitor Cohort (participant with on-demand therapy) and Non-Inhibitor Cohort (participants with on-demand therapy): The analysis of each endpoint in this group aims to demonstrate superiority of PF-06741086 prophylaxis over *on-demand* treatment. Criterion for declaring superiority will be described in the SAP. • The following bleeding incidence endpoints will be analyzed using the same repeated measures negative binomial model via GEE as in the primary analysis, and treatment effect expressed as the ratio of bleeding event rates: incidence of joint bleeds;

Endpoint	Statistical Analysis Methods
	incidence of spontaneous bleeds; incidence of target joint bleeds; and the incidence of total bleeds (treated and untreated). • Change from baseline in the HJHS will be compared using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference. • Change from baseline in Haem-A-QoL/Haemo-QoL, HAL/pedHAL, and EQ-5D-5L will be compared using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference. • PGIC-H will be compared using the Wilcoxon signed rank test (within-participant comparison), with treatment effect estimated as the median difference. <u>Non-Inhibitor Cohort (participants with routine prophylaxis therapy)</u>: The analysis of each endpoint in this group in general aims to demonstrate non-inferiority of PF-06741086 prophylaxis over routine *prophylaxis*. For those endpoints that will be used for labeling with a goal of demonstrating non-inferiority of PF-06741086 prophylaxis, the non-inferiority margin will be derived in the SAP. After establishing non-inferiority, subsequent testing of superiority may be conducted. • The following bleeding incidence endpoints will be analyzed using the same repeated measures negative binomial model via GEE as in the primary analysis, and treatment effect expressed as the difference in bleeding event rates: incidence of joint bleeds; incidence of spontaneous bleeds; incidence of target joint bleeds; and the incidence of total bleeds (treated and untreated). • Change from baseline in the HJHS will be compared using the Wilcoxon signed rank test. • Change from baseline in Haem-A-QoL/Haemo-QoL, HAL/pedHAL and EQ-5D-5L will be compared using the Wilcoxon signed rank test. • PGIC-H will be compared using the Wilcoxon signed rank test. Participants with inhibitors with routine prophylaxis has the same set of secondary endpoints and will be separately summarized using descriptive statistics without any hypothesis testing or inferential statistics.
Exploratory	Will be described in the SAP finalized before database lock

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	• Descriptive analyses of AEs, ECGs, vital signs (blood pressure, pulse rate, temperature and respiratory rate), physical examinations and safety laboratory data (including hematology, PT/INR, aPTT, chemistry, urinalysis, fibrinogen, anti-thrombin III activity and cTnI) will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Safety data will be presented in tabular or graphical format and summarized descriptively, where appropriate. Incidence and severity of TEAEs, withdrawals due to TEAEs, and non-study intervention infusion and study intervention injection site reactions will be

Endpoint	Statistical Analysis Methods
	summarized by cohort. Abnormal and clinically relevant changes in vital signs and ECG parameters will be summarized by cohort and study day. Incidence and magnitude of abnormal laboratory findings will be summarized by cohort. • Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay. Frequencies of ADA and NAb will be summarized by cohort and study day for samples collected.
Exploratory	Will be described in the SAP finalized before database lock

9.4.2.1. Electrocardiogram Analyses

ECG parameters will be summarized.

9.4.3. Other Analyses

PK, PD, and biomarker exploratory analyses will be described in more detail in the SAP finalized before database lock. The population PK analysis and PK/PD analyses will be presented separately from the main CSR.

In the event a full dose cannot be administered, a partial dose will be reported, and partial doses will be imputed using 50% of the full dose for each injection.

9.5. Interim Analyses

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

Throughout the study, the eDMC will assess the overall benefit-risk.

9.5.1. External Data Monitoring Committee (eDMC)

This study will use an eDMC. The eDMC is independent of the study team and includes only external members. The eDMC charter describes the role of the eDMC in more detail.

The primary rationale for establishing the committee is to ensure that appropriate external safeguards are in place to oversee the safety of participants enrolled in this study and to maintain scientific rigor with respect to accumulating safety data while the trial is ongoing. In addition to overall safety review, the committee will focus on evaluation of thrombotic events, injection site reactions and abnormal cTnI laboratory data as well as ECG and clinical data associated with cTnI elevations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, IB, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
    - In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.
    - In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (defined as a parent, guardian, or other legally authorized representative as defined by local standards) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The investigator must ensure that each study participant or his legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his legally authorized representative is fully informed about his right to access and correct his personal data and to withdraw consent for the processing of his personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be re-consented to the most current version of the ICD(s) during their participation in the study.

Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICD.

The ICD will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature *(for Japan country changes refer to Appendix 7: Country-specific requirements)*.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

For France sites, please refer to country-specific appendix (Section 10.7.2).

10.1.5. Committee Structure

The eDMC will be responsible for ongoing monitoring of safety of participants in the study according to the Charter. The eDMC will consist of a chairperson and up to 5 additional members including at least 2 with medical qualifications in hematology, 1 to 2 with medical qualifications in cardiology, and at least 1 other who is a statistician. The eDMC will review unblinded individual participant data in addition to aggregate data.

The eDMC will review accumulating safety data from this study on a regular basis, approximately every 6 months. The study team and the eDMC can request additional safety

data reviews as they see fit and ad hoc meetings will be arranged to accommodate these reviews. During meetings the eDMC will review unblinded safety data.

Based on these reviews, the eDMC will have the capacity to make recommendations to the study team that might impact the future conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study, or continuing the study as designed. In addition, the eDMC may be provided with safety, PK/PD and exploratory biomarkers data from the ongoing or completed studies. The details around the conduct and responsibilities and roles of the eDMC will be provided in the DMC Charter.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the EU Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Monitoring Plan.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to contract research organization if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card and instructed to always carry the contact card and present to medical personal if medical treatment is required. The contact card contains, at a minimum, protocol and investigational product identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer Clinical Research Unit, the contact number is not intended for use by the participant directly, and if a participant calls that number, he will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the SoA will be analyzed by the central laboratory. In addition, FVIII activity and FIX activity may be analyzed at a local laboratory instead of the central laboratory. Samples for cTnI (where available) assessments will also be analyzed at the local AND central laboratories at each timepoint.

For adolescent participants, the following "Best Practices" for pediatric blood collection include:

1. Instruct parents to ensure child is well-hydrated prior to blood collection.
2. Keep the child warm throughout the process of preparing for and drawing blood.
3. Consider warming the area of the venipuncture site with a heat pack or warm cloth.
4. A lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to blood collection to decrease potential discomfort to the participant. The anesthetic must not contain propylene glycol. The skin must be thoroughly cleansed prior to blood sample collection. It is recommended that 2 venipuncture sites be prepared with local anesthetic in case the first attempt is not successful.
5. Use appropriate needle gauge for size of participant.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

10.2.1. Central Laboratory

The following formulae will be utilized by the central laboratory for the calculation of eGFR:

Modification of Diet in Renal Disease (MDRD) for adults ≥18 years of age:

Calculation Name: Ⓢ	GFR by MDRD	
Formula	**Units**	**Decimal Places**
Conventional: 175 x Serum Creatinine (mg/dL) $^{-1.154}$ x Age $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)	mL/min/1.73m^2	1
SI: 175 x (Serum Creatinine (umol/L) x 0.01131) $^{-1.154}$ x Age $^{-0.203}$ x 1.212 (if Black) x 0.742 (if Female)	mL/min/1.73m^2	1

For adolescents <18 years of age[20]:

Calculation Name: (S) Creat Clear Ped Schwartz		
Formula	**Units**	**Decimal Places**
Conventional: **<1 years:** (0.45 x Height (cm))/serum creatinine (mg/dL) **1-13 years:** (0.55 x Height (cm))/serum creatinine (mg/dL) **Females 13-18 years:** (0.55 x Height (cm))/serum creatinine (mg/dL) **Males 13-18 years:** (0.70 x Height (cm))/serum creatinine (mg/dL)	mL/min/1.73m^2	0
SI: **<1 years:** (0.45 x Height (cm))/serum creatinine (umol/L) x (0.01131) **1-13 years:** (0.55 x Height (cm))/(serum creatinine (umol/L) x (0.01131) **Females 13-18 years:** (0.55 x Height (cm))/serum creatinine (umol/L) x (0.01131) **Males 13-18 years:** (0.70 x Height (cm))/serum creatinine (umol/L) x (0.01131)	mL/min/1.73m^2	0

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: o Is associated with accompanying symptoms. o Requires additional diagnostic testing or medical/surgical intervention. o Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious.

- The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AE and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical

terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding.	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE).**
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories using the CTCAE Version 5.0:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgement to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it**

is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally submitted documents.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

No contraception methods are required for male participants in this study as there is no risk of teratogenicity/fetoxicity.

Collection of Pregnancy Information:

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

A female becomes, or is found to be, pregnant either having been exposed (eg, because of treatment or environmental exposure) to the investigational product;

- An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a

live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.The participant should return to the investigator site and be evaluated as soon as possible, preferably within

48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's Law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6.1.1 for the list of sponsor medical devices).

10.6.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2; see Appendix 7 definition of SADE for Japan).
SADE Definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition
• A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis management file (see Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.6.4. Recording/Reporting and Follow-up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and will also capture the required information on the Medical Device Complaint form. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the Medical Device Complaint form. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. Requirements for recording and reporting an AE or SAE are provided in Appendix 3 (Section 10.3.3). • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.   ○ A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of

a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB or product information, for marketed products, in his/her assessment.
- For each device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements

Follow-up of Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements or evaluations as medically indicated or as requested by the sponsor to elucidate the nature or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form.

- New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety on the CT SAE Report Form within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.6.5. Reporting of SAEs

Reporting of an SAE to Pfizer Safety must be performed according to the processes described in Appendix 3 (Section 10.3.4).

10.6.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs (ie, a SADE) that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

10.7. Appendix 7: Country-specific Requirements

10.7.1. Japan Appendix

For the investigator sites in Japan only:

Underlined text added in place of strike-through

Japan SADE Definition

A SADE is defined as an Incident associated with a device, and the Incident was such that, if it occurred again, might lead to death or a serious deterioration in health (see Section 10.6.2 for the definition for SADE).

Section 1.3. Schedule of Activities (SoA)

Active Treatment Phase (ATP); Visit 10; PF-06741086 sample collection

For adolescent participants in Japan, this sample (PF-06741086 at Visit 10) will only be collected from adolescent participants with a body weight >40 kg.

Section 6.5.3. Treatment of Breakthrough Bleeding

For participants with inhibitors who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or treating physician requires additional hemostatic therapy beyond PF-06741086 prophylaxis rFVIIa or FEIBA are allowable. ~~rFVIIa may be administered at the lowest effective dose but not to exceed 90 µg/kg per dose and not to exceed a dosing frequency of approximately every 2 hours.~~For the participants in Japan, rFVIIa should be used with approved dosage in Japan, the first dose should be 90 µg/kg and the second or later dose should be 60~90 µg/kg and not to exceed a dosing frequency of approximately every 2 hours.

The investigator should confirm participant's understanding at the beginning of the trial regarding the determination of the necessity of administration of hemostatic treatment for breakthrough bleeding and the appropriate dosage. Whenever possible, before the participant or parent/caregiver administers the drug for breakthrough bleeding episodes, the participant should contact the investigator to confirm the necessity of the hemostatic treatment.

Section 8. Study Assessments and Procedures

Blood Collection and Approximate Blood Volume (Participants in Japan Only)

The maximum planned amount of blood collected from each adult participant with hemophilia A in Japan over the duration of the study should not exceed approximately 354 mL, the maximum planned amount of blood collected from each adult participant with hemophilia B in Japan over the duration of the study should not exceed approximately 333 mL, and the maximum planned amount of blood collected from each adolescent participant over the duration of the study should not exceed approximately 277 mL (based on

Screening through ATP Visit 20). The total blood volumes over the duration of the study are estimated based on sample volumes in the laboratory manual. The actual collection times of blood sampling may change. Additional blood samples may be taken from adult participants for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days. Total blood volume taken from adolescent participants must comply with EMA Guidance entitled, "Ethical considerations for clinical trials on medicinal products conducted with minors."[19]

Section 10.1.3. Informed Consent Process

Additional text added:

For Japanese minor participants (under 20 years of age before 31 March 2022, under 18 years of age after 01 April 2022), it is necessary that the participant's parent or a caregiver, etc. sign the informed consent form, regardless of whether the participant has signed the assent document.

10.7.2. France Appendix

Contrat Unique

5. GCP Training
   Before enrolling any participants, the investigator and any sub-investigators will complete the Pfizer provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.
6. Study Intervention
   No participants or third-party payers will be charged for study intervention.
7. Urgent Safety Measures
   In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.
8. Termination Rights
   Pfizer retains the right to discontinue development of marstacimab at any time.

Section 10.1.4. Data Protection

Additional text added:

The study sponsor, Pfizer Inc., and the study doctor/hospital undertake to process your collected data in compliance with Regulation (EU) 2016/679 of the European Parliament and

of the Council of the 27 April 2016 applicable on 25 May 2018 (GDPR) and the data protection laws of France.

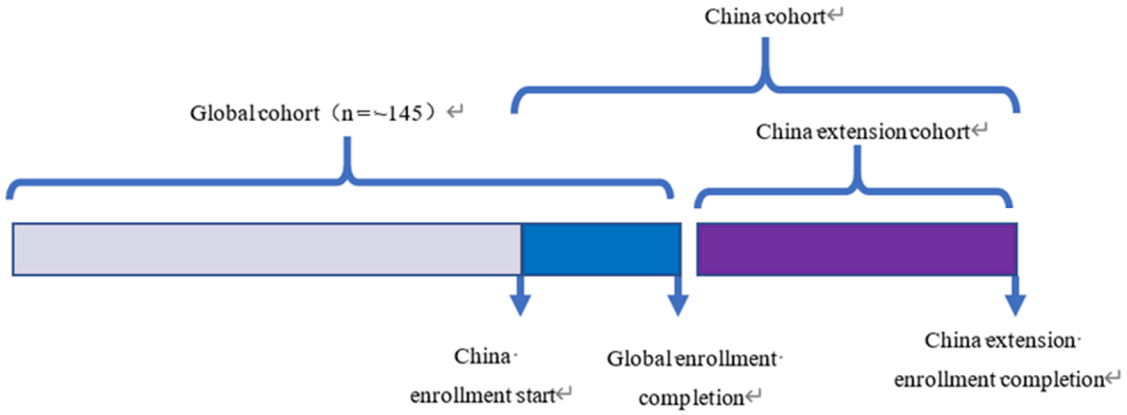
10.7.3. China Appendix

This appendix is relevant only to study sites located in China.

Approximately [redacted] % of the overall planned enrollment into Study B7841005, which has an anticipated sample size of approximately 145 global participants, will come from China per local registration requirements.

Study B7841010 is the ongoing local Chinese PK study that is scheduled to enroll up to 6 participants. These participants will be eligible to roll into the global enrollment pool in Study B7841005, assuming they meet all study entry criteria and global enrollment has not been achieved. In addition, considering that global enrollment into Study B7841005 may be completed prior to enrollment of additional Chinese participants, local participants will also continue to be randomized into a China extension cohort after the study has achieved its global enrollment targets. Local Chinese B7841005 study participants enrolled during global enrollment and in the China extension cohort will be pooled together to form the China cohort (see Figure 2).

Figure 2. China Cohort



Participants enrolled in the China Extension cohort will be analyzed for the purpose of registration in China only. Data analysis of the global trial will not include participants enrolled in the China Extension cohort. The details of the analysis will be provided in the SAP.

Section 8. Study Assessments and Procedures

Blood Collection and Approximate Blood Volume (Participants in China Only)

The maximum planned amount of blood collected from each adult participant in China over the duration of the study should not exceed approximately 367 mL and the maximum planned amount of blood collected from each adolescent participant over the duration of the study should not exceed approximately 261 mL (based on Screening through ATP Visit 20).

The total blood volumes over the duration of the study are estimated based on sample volumes in the laboratory manual. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken from adult participants during the study does not exceed 550 mL during any period of 30 consecutive days. Total blood volume taken from adolescent participants must comply with EMA Guidance entitled, "Ethical considerations for clinical trials on medicinal products conducted with minors."[19]

10.8. Appendix 8: Abbreviations

Abbreviation	Term
ABR	annualized bleeding rate
ADA	anti-drug antibody
ADE	adverse device effect
AE	adverse event
AESI	adverse event of special interest
AIFA	Italian Medicines Agency
ALT	alanine aminotransferase
AP	Active Treatment Phase
aPCC	activated Prothrombin Complex Concentrates
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	Active Treatment Phase
AV	atrioventricular
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CDE	(China) Center for Drug Evaluation
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	case report form
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	cardiac troponin I
CT SAE	Clinical Trial Serious Adverse Event
DILI	drug-induced liver injury
dPT	dilute prothrombin time
DRE	disease-related event
EC	ethics committee
ECG	electrocardiogram
eDiary	electronic Diary
eDMC	external data monitoring committee
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMA	European Medicine Agency
ePRO	electronic patient reported outcome

Abbreviation	Term
EQ-5D	EuroQol 5 Dimensions
EQ-5D-5L	EuroQol 5 Dimensions 5 Level
EU	European Union
FDA	Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FIH	first in human
FIX	factor IX
FVIIa	tissue factor-activated coagulation factor VII
FVIII	factor VIII
FXa	activated factor X
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	generalized estimating equation
GGT	gamma-glutamyl transferase
Haem-A-QoL	Hemophilia Quality of Life Questionnaire for Adults
Haemo-QoL	Hemophilia Quality of Life Questionnaire for Children
HAL	Hemophilia Activities List
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HLIQ	Hemophilia Life Impacts Questionnaire
HPRA	The Health Products Regulatory Authority
HRQoL	health-related quality of life
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgG1	Immunoglobulin G isotype, subclass 1
IMP	investigational medicinal product
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
IVIG	intravenous immunoglobulin
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
LLN	lower limit of normal
MDRD	Modification of Diet in Renal Disease
MFDS	Ministry of Food and Drug Safety
mITT	modified intent-to-treat
MMRM	Mixed-effects Model with Repeated Measures

Abbreviation	Term
N	total number of participants
NAb	neutralizing antibody
NIMP	non-investigational medicinal product
OP	Observational Phase
PACL	Protocol Administrative Change Letter
PCC	Prothrombin Complex Concentrates
PCD	primary completion date
pedHAL	Pediatric Hemophilia Activities List
PD	pharmacodynamics(s)
PDCO	Paediatric Committee
PEI	Paul Ehrlich Institute
PF1+2	prothrombin fragment 1+2
PGIC-H	Patient Global Impression of Change - Hemophilia
PIN	personal identification number
PK	pharmacokinetic(s)
PKT	peak thrombin
PMDA	Japan Pharmaceuticals and Medical Devices Agency
PRO	patient reported outcome
PT	prothrombin time
QM	once monthly
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QW	once weekly
RA	Regulatory Authority
RBC	red blood cell
rFVIIa	recombinant factor VIIa
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCr	serum creatinine
SD	standard deviation
SoA	Schedule of Activities
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
UK EC	United Kingdom Ethics Committee
ULN	upper limit of normal

Abbreviation	Term
US	United States
USADE	unanticipated serious adverse device effect
VRS	verbal rating scale
WBC	white blood cell

10.9. Appendix 9: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 beats per minute [bpm]) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer;
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
• Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (heart rate 40 bpm to

<100 bpm), and monomorphic/polymorphic ventricular tachycardia (heart rate >100 bpm, such as torsades de pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.10. Appendix 10: Bleeding Definitions[21,22]

This following is a list of definitions used in this protocol to define bleeds or bleeding episodes:

Definition of a Bleed:

Bleed: A bleed is classified in this study as either "spontaneous" or "traumatic". The criteria for spontaneous and traumatic bleeding episodes are described in this appendix (below). Any sign or symptom of a bleed, regardless of whether or not medication/treatment is administered, should be reported as a "bleed" or "bleeding episode".

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

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

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

Definition of a Bleed Sites:

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

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

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

Definition of Bleed Types:

Spontaneous Bleeds: Bleeding for no apparent/known reason particularly into the joints, muscles, and soft tissues.

Traumatic Bleeds: Bleeding event occurring for an apparent/known reason.

Note: Bleeds related to a procedure/surgery such as hematomas/bruising resulting from any surgeries or invasive procedures (eg, tooth extractions, venipuncture, or subcutaneous drug

administrations) or invasive diagnostic procedures (eg, lumbar puncture, endoscopy with biopsy) would NOT be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

10.11. Appendix 11: Derivation of Non-Inferiority Margin for Treated Bleeds

The derivation followed the methodology outlined in FDA (Food and Drug Administration) Guidance for Non-Inferiority Clinical Trials to Establish Effectiveness.[23]

Historical data were selected among Pfizer 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 12-74 years old to match Study B7841005 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 one-way crossover study intended to compare the efficacy and safety between the on-demand treatment and prophylactic therapy using BeneFIX in hemophilia B participants with ages 12-65 years old and the FIX activities not greater than 2%. This study comprised Period 1 (on-demand treatment at a dosage determined by principal investigator, 6 months) and Period 2 (100 IU/kg once-weekly dose, 12 months).

B1821002 was an open-label, randomized, four-period crossover study on males with hemophilia B with ages 6-65 years old and the FIX activities not greater than 2% to compare on-demand administration and two prophylaxis regimens. Study was conducted 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 safety and efficacy of ReFacto AF in hemophilia A participants switching to ReFacto AF from ReFacto or other FVIII products in usual care settings. The participants were of ages 12 and greater and had FVIII activities <1%. All participants were treated under standard care with ReFacto AF at a dose and frequency prescribed by the treating physician. The duration of treatment depended on the frequency of infusions (to achieve 100 exposure days) with mean standard deviation (SD) of 336 (223) days.

Table 3 presents analyses of the ABR of treated bleeds of participant level data from three Pfizer hemophilia studies with inclusion/exclusion criteria that closely matched those for Study B7841005. The analyses included participants with matching age (12-74 years old) and factor level (<1%) criteria to Study B7841005. The mean ABR difference between prophylaxis and on-demand treatment was estimated using three analyses: t-test allowing for non-homogeneous variances, Hodges-Lehmann 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 two-sided 95% CIs ranging from 16.8 to 17.6.

Table 3. Analyses of Bleeding in Three Pfizer Hemophilia Studies Used in Deriving the Non-Inferiority Margin

	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 Lehmann	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)

1: Model-based from negative binomial regression
2: Negative binomial regression
Notes:
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

Based on the lower bound of the confidence interval of this estimate, the on-demand ABR was assumed to be higher by at least 16.8, which was considered M_1 in the non-inferiority test setting.

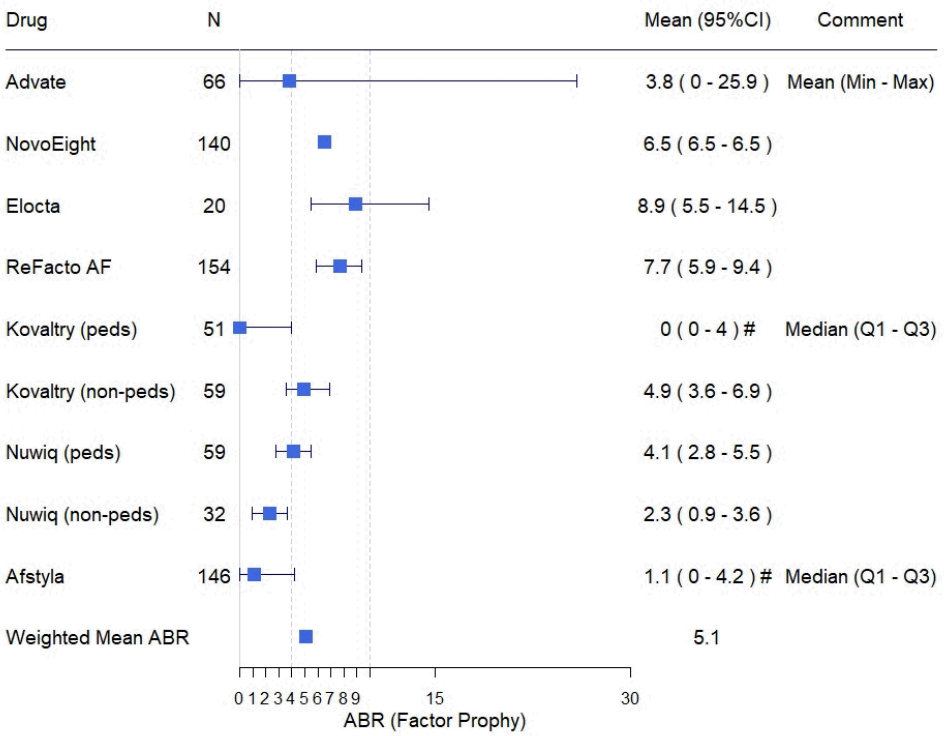
Given the large effect size of prophylaxis treatment, an appropriate value for M_2 was considered in order to preserve a sufficiently large proportion of this effect. A value of 2.5 for M_2 (~85% effect preserved) was selected as both clinically meaningful and yielding a reasonable sample size. M_1 and M_2 are derived from the notation used in the FDA Guidance document, Non-Inferiority Clinical Trials to Establish Effectiveness.[23]

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

Non-inferiority Margin.[24] In particular, the margin of 2.5 establishes acceptable efficacy relative to the active comparator predicated in Section 4 of the aforementioned guideline:

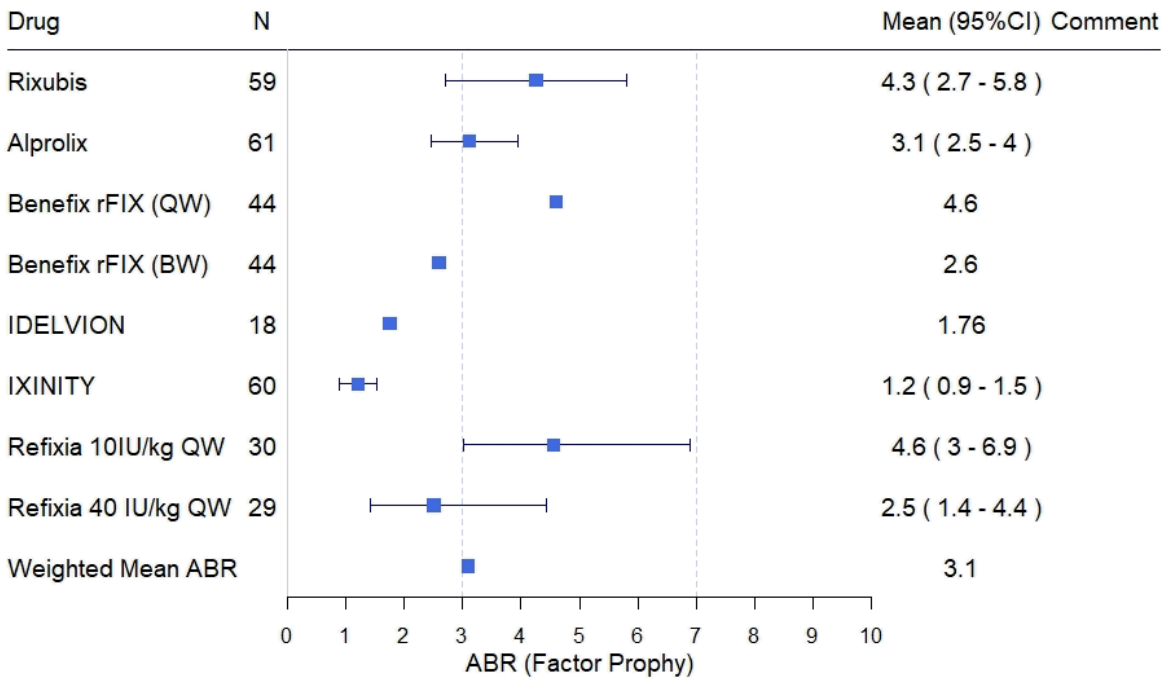
- The estimated effect of factor replacement therapy vs on-demand and its most conservative lower bound of the 95% CI is ~21 ABR and 16.8, respectively.
- The margin of 2.5 preserves 85% of the most conservative estimated effect of 16.8.
- In meta-analyses of factor replacement products to 2017, the weighted mean ABR was 5.1 for FVIII prophylaxis (Figure 3) and 3.1 for FIX prophylaxis (Figure 4); for FIX prophylaxis, all products have participants with factor level activity ≤2%, the planned Phase 3 <1%; therefore, the non-inferiority margin of 2.5 should be interpreted in the background comparator mean ABR of ~4.5.
- Expected half-width of 95% CI is 2.1 applying the parameter assumptions for the sample size calculation (ABR of 2.5 for 6 months for prior prophylaxis, 4 for one year for PF-06741086 prophylaxis, variance = 6*mean, correlation = 0.2); therefore meeting the non-inferiority margin of 2.5 requires that the point estimate for the difference is close to 0; further establishing acceptable efficacy of PF-06741086 relative to factor replacement therapy.
- In addition, PF-06741086 has an advantage via once weekly subcutaneous dosing vs up to 2 or 3 times weekly IV dosing of the active comparators. Per guidance, it may be possible to justify a wider non-inferiority margin for efficacy in this case.

Figure 3. Results for Prophylaxis with FVIII Products (to 2017)



The sources are the FDA summary basis of approvals for all factor replacement therapies that were approved post 2010 in the United States as well as Pfizer internal data (ReFactoAF).

Figure 4. Results for Prophylaxis with FIX Products (to 2017)



The sources are the FDA summary basis of approvals for all factor replacement therapies that were approved post 2010 in the United States.

Clinically, the planned non-inferiority hypothesis will be met if the difference between PF-06741086- and factor-based prophylaxis regimens does not exceed 2.5. The pooled ABR observed across the 4 cohorts studied in the three month Phase 2 B7841002 study of PF-06741086-based prophylaxis was 2.6 (N=24).[25] Reproducing this result in Study B7841005 during the active treatment period, and assuming a factor-based prophylaxis ABR of ~4.5 during the observation period, would place the upper bound of the 95% confidence interval (CI) difference at around an ABR of 5, which is comfortably within the range of ABR achieved with approved FVIII- and FIX-based prophylaxis regimens depicted in Figure 3 and Figure 4.

10.12. Appendix 12: Alternative Study Procedures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.12.1. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit as of Active Treatment Phase (ATP) Visit 8 (ie, Day 7 Visit), study sites are permitted to defer the conduct of the procedures, listed below, to the home health/mobile phlebotomy services or local medical establishments, provided that local regulations permit:

- All protocol required lab draws.
- Weight and vital signs (eg, body temperature, BP, pulse rate, respiratory rate).
- Patient-Reported Outcomes Questionnaires.
- Investigational Medication Dispensing and Accountability.
- Physical exam/brief physical exam.
- Electrocardiogram.

In the event that an in-clinic visit cannot be completed due to the COVID-19 pandemic, it is understood that the procedures, like the ones listed below, may not be able to be performed. In such cases, you should document the reason for the missed test (eg, in-clinic visit missed due to COVID-19 restrictions) on the case report form.

- Hemophilia Joint Health Score (HJHS).
- Patient-Reported Outcomes Questionnaires.

10.12.2. Telehealth Visits

In the event that in-clinic visits cannot be conducted, every effort should be made to follow-up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software)

remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any new concomitant medications or changes in concomitant medications since last contact.
- Review and record any AEs and SAEs since last contact, including but not limited to COVID-19 related events. The AE and SAE reporting process should be followed per protocol (Section 8.3).
- Review bleeding episodes and factor or bypass infusions reported in the eDiary.
- Dose Escalation Assessment (starting Visit 14, ATP Day 180).
- Arrangements made for Investigational Medication resupply, when applicable.

Study participants must be reminded to promptly notify site staff about any change in their health status.

If the participant or caregiver has any concerns regarding his safety and an in-clinic or unscheduled study visit cannot be performed due to public emergencies, including COVID-19 pandemic-related issues, then the participant should visit his primary care physician or local clinic for an evaluation and appropriate medical treatment. The participant or caregiver should request that the medical provider consult with the study PI regarding this medical visit so appropriate medical care can be coordinated in accordance with the participant's ongoing participation in this study, B7841005.

10.13. Appendix 13: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 6, 13 July 2021

The amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:

The protocol was amended: a) to add a country-specific amendment to enable China to meet CDE registration enrollment requirements by an allowance to continue to enroll participants in China after global enrollment is completed; b) to allow additional participants (approximately 20%) in order to provide sufficient enrollment into regions which have experienced delays created by the COVID-19 global pandemic; c) changes made to reflect the change of inclusion criteria for hemophilia B to include participants with factor IX levels ≤2%, in line with the currently available EMA guideline (clinical investigation of recombinant and human plasma-derived factor IX products) and to enable recruitment of hemophilia B participants and participants with inhibitors based on recruitment challenges and feedback received from clinical study sites; d) added edits based on a unanimous eDMC recommendation that treatment with study intervention is to be suspended if a participant develops a presumed or confirmed symptomatic COVID-19 infection due to the potential for thrombotic events; e) added changes to the estimated total blood volume and maximum allowed blood volume collection following central laboratory specification revisions; f) AESIs, injection site reactions, and thrombotic events were added to protocol Section 8.3.8 Adverse Events of Special Interest. These were not previously included due to edits resulting from internal review to simplify protocol procedures, to clarify instructions, and to correct errors. Editorial updates were made throughout the document.

Substantial protocol amendment changes are tabulated below. Text that has been deleted is shown with strikethrough and text that been added is shown as underlined.

Section # and Name	Description of Change	Brief Rationale
Title page; Section 1.1 Synopsis	Protocol Title changed: An Open-Label Study in Adolescent and Adult Severe (Coagulation Factor Activity <1%) Hemophilia A ~~or B Patients~~ Participants With or Without Inhibitors or Moderately Severe to Severe Hemophilia B Participants ~~Patients~~ (Coagulation Factor Activity ≤2%) With or Without Inhibitors Comparing Standard Treatment to PF-06741086 Prophylaxis	Title revised to align with updated inclusion criteria to enable recruitment of hemophilia B participants and participants with inhibitors based on recruitment challenges and

Section # and Name	Description of Change	Brief Rationale
		feedback received from clinical study sites.
Section 1.1 Synopsis; Section 3 Objectives, Estimands, and Endpoints	Revised primary objective: To demonstrate the efficacy and safety of PF-06741086 for routine prophylaxis in severe hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤~~<~~1~~2~~%, respectively) ~~hemophilia A or B~~ participants 12 to <75 years of age with or without inhibitors Revised primary efficacy endpoint text: Inhibitor Cohort (participants with prior on-demand therapy): In all regions, to demonstrate superiority in ABR of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus on-demand treatment with bypass therapy during the 6 months prior to receiving study intervention. Non-Inhibitor Cohort: For regions outside of the EU, superiority in ABR of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus on-demand treatment with FVIII- or FIX- replacement during the Observational Phase prior to receiving study intervention (note this is a secondary endpoint for the EU). For the EU, non-inferiority in ABR of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus prophylaxis treatment with FVIII- or FIX-replacement during the Observational Phase prior to receiving study intervention (note this is a secondary endpoint for regions outside the EU). Revised secondary objective endpoint text: For the Non-Inhibitor Cohort, the primary endpoint with respect to comparisons with prior on-demand therapy for regions outside EU will be a secondary endpoint for the EU. Likewise, the primary endpoint with respect to comparisons with prior prophylaxis therapy for the EU will be a secondary endpoint for the regions outside EU. The following parameters will be assessed for comparison between PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase versus a respective control group corresponding to each of the 3 statistical objectives (inhibitors [participants with prior on-demand therapy], non-inhibitors [with prior on-demand therapy], and non-inhibitors [with prior prophylaxis therapy]).	Primary objective revised to align with updated inclusion criteria to enable recruitment of hemophilia B participants and participants with inhibitors with prior prophylaxis based on recruitment challenges and feedback received from clinical study sites. The notes were added for clarification. All revisions in the secondary objective endpoint text were for clarification.

Section # and Name	Description of Change	Brief Rationale
	objectives (inhibitors, [participants with on-demand therapy], non-inhibitors ~~for regions outside EU,~~[with prior on-demand therapy], and non-inhibitors ~~for the EU). For the Non-Inhibitor Cohort, all the primary and secondary endpoints for regions outside of the EU will be part of the secondary endpoints for the EU and vice versa.~~[with prior prophylaxis therapy]).	
Section 1.1 Synopsis, Overall Design; Section 2 Introduction; Section 4.1 Overall Design; Section 4.2 Scientific Rationale for Study Design; Section 5.1 Inclusion Criteria 2	…severe hemophilia A or moderately severe to severe hemophilia B (defined as factor VIII [FVIII] activity <1% or factor IX [FIX] activity ≤~~<1~~2%, respectively) …	Aligned with updated inclusion criteria to enable recruitment of hemophilia B participants and participants with inhibitors based on recruitment challenges and feedback received from clinical study sites. These changes are intended to partially relax the inclusion criteria for hemophilia B to be inclusive of participants with moderate severity based on baseline factor activity level and hemorrhagic phenotype.
Section 1.1 Synopsis, Overall Design; Section 4.1 Overall Design	Added text: 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 (see Section 9.2 Sample Size Determination for additional details). Prior Prophylaxis Treatment: Participants without inhibitors who were on prior prophylactic treatment with FVIII- or FIX-replacement during the Observational Phase will transition to the Active Treatment Phase after approximately 6 months. Participants with inhibitors who are on routine prophylaxis (defined as treatment by IV injection of bypass agent to prevent bleeding) may be considered for eligibility on a case-by-case basis at the discretion of the sponsor, following discussion and agreement from the Pfizer medical monitor. These participants will be included in	Added allowance for additional participants so as to provide additional time for participants to be enrolled in countries which had difficulties enrolling due to the COVID pandemic. Aligned with updated inclusion criteria to enable recruitment of participants with

Section # and Name	Description of Change	Brief Rationale
	addition to the On-Demand Inhibitor participants and will supplement the safety evaluation of the inhibitor cohorts. Approximately [redacted]% of the overall planned enrollment into Study B7841005, which has an anticipated sample size of approximately 145 global participants, will come from China per local registration requirements. Study B7841010 is the ongoing local Chinese PK study that is scheduled to enroll up to 6 participants. These participants will be eligible to roll into the global enrollment pool in Study B7841005, assuming they meet all study entry criteria and global enrollment has not been achieved. In addition, considering that global enrollment into Study B7841005 may be completed prior to enrollment of additional Chinese participants, local participants will also continue to be randomized into a China extension cohort after the study has achieved its global enrollment targets. Local Chinese B7841005 study participants enrolled during global enrollment and in the China extension cohort will be pooled together to form the China cohort and will be analyzed to support the registration in China only (for China country changes refer to Appendix 7: Country-specific Requirements). Data analysis of the global trial will not include participants enrolled in the China extension cohort.	inhibitors based on recruitment challenges and feedback received from clinical study sites. To allow sufficient participants to be enrolled in China to meet CDE registration requirements.
Section 1.2 Schema; Section 4.1 Overall Design	Phase 3 Study Schematic footnotes revised	Revised for competitive enrollment as the numbers in the main schematic fulfill efficacy and safety requirements.
Section 4.2 Scientific Rationale for Study Design	Similarly, limiting inclusion to only those with at least 6 bleeding or at least 4 bleeding episodes for hemophilia A and B, respectively in the 6 months prior to screening is recommended because these are the participants who would be expected to show therapeutic benefit.	Aligned with updated inclusion criteria to enable recruitment of hemophilia B participants based on recruitment challenges and feedback received from clinical study sites.
Section 5.1 Inclusion Criteria	Inclusion Criteria 4 • Hemophilia A p~~P~~articipants with on-demand treatment regimen with ≥6 bleeding episodes or hemophilia B participants with ≥4 bleeding episodes (spontaneous or traumatic) necessitating treatment with bypass factor during the 6 months prior to Enrollment into Observational Phase and willing to continue to receive on-demand	Updated inclusion criteria to enable recruitment of hemophilia B participants based on recruitment challenges and feedback received

Section # and Name	Description of Change	Brief Rationale
	treatment during the Observational Phase. Surgical bleeding episodes do not apply to this criterion. • Participants who meet the bleeding criteria noted above and who are on routine prophylaxis (defined as treatment by IV injection of bypass factor to prevent bleeding) and have demonstrated at least 80% compliance with scheduled prophylaxis regimen during the 6 months prior to enrollment, may be considered for eligibility on a case-by-case basis with discussion and agreement from the Pfizer medical monitor.	from clinical study sites. These changes are intended to partially relax the inclusion criteria for hemophilia B to be inclusive of participants with moderate severity based on baseline factor activity level and hemorrhagic phenotype.
Section 5.2 Exclusion Criteria	Exclusion Criteria 9. Current routine prophylaxis with bypassing agent (eg, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa), non-coagulation non-factor replacement therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of 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 non-factor-based hemophilia therapy (eg, fitusiran, concizumab, emicizumab) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer medical monitor. Exclusion Criteria 11. Ongoing or planned use of immune tolerance induction during the Observational Phase or Active Treatment Phase, or prophylaxis with FVIII or FIX replacement at any time after initiation of treatment with study intervention during the Active Treatment Phase.	Text reformatted and aligned with updated inclusion criteria to enable recruitment of participants with inhibitors based on recruitment challenges and feedback received from clinical study sites. The text “at any time after initiation of treatment with study intervention” added to provide clarification.
Section 6.5.2.2 Active Treatment Phase	Added under “Non-Inhibitor Cohort”: • Prophylaxis treatments with regularly prescribed hemostatic medication are permitted until initiation of treatment with study intervention at Visit 7. Added under “Inhibitor Cohort”: • When agreed between investigator and Pfizer medical monitor, current routine prophylaxis with bypassing agent are permitted until initiation of treatment with study intervention at Visit 7.	Modified due to investigator feedback to allow schedule prophylaxis doses until the first day of study intervention administration.
Section 7.1 Discontinuation	Added: Treatment with PF-06741086 will be suspended for any participant who has entered the Active Treatment Phase and has	New text requested by

Section # and Name	Description of Change	Brief Rationale
of Study Intervention, Interruption or Dose Modification	presumed or confirmed, symptomatic COVID-19, regardless of severity grade of the associated AE. The differential diagnosis of COVID-19 is based on the investigator's medical judgement and ideally should be confirmed by a positive SARS-Cov-2 test; however, this test is not required. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed.	external Data Monitoring Committee.
Section 8 Study Assessments and Procedures	Updated blood collection volumes in text and Table 2. Added references to Japan- and China-specific blood collection and volume information in Appendix 7.	Updated lab sample volumes due to central laboratory vendor COVID pandemic-related supply chain challenges and to align with EMA guidance for pediatric blood volume collection.
Section 8.3.8 Adverse Events of Special Interest	~~Not applicable.~~ Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. AESIs for this study are AEs, "injection site reactions" and "thrombotic" events, as well as AEs requiring continuous monitoring (eg, additional laboratory testing) or requiring treatment modification (eg, delay or discontinuation of study intervention). For any participant who develops a thrombotic AE or an AE requiring treatment modifications, please refer to Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal, Individual Level Stopping and Dose Adjustment Rules for conditions under which participants continued administration of study intervention may be discontinued or suspended. All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.	AESIs added as these were omitted in prior versions of the protocol.
Section 9.1 Estimands and Statistical Hypotheses	Inhibitor Cohort (participants with prior on-demand therapy): in all regions, to demonstrate superiority of PF-06741086 prophylaxis observed over a 12-month Active Treatment Phase relative to ~~routine~~ on-demand treatment during the 6 months prior to receiving study intervention, on the ratio of the ABR of treated bleeds using a repeated measures model to account for participant′s experience in the OP and ATP, in participants ≥12 years of age with severe	Wording changes aligned with updated inclusion criteria in participants with inhibitors–hemophilia B participants and

Section # and Name	Description of Change	Brief Rationale
	hemophilia A or moderately severe to severe hemophilia B (FVIII activity <1% or FIX activity ≤2%, respectively) ~~hemophilia (coagulation factor activity <1%) A or B~~ with inhibitors who receive ~~routine~~ on-demand treatment during the 6 months prior to receiving study intervention. Superiority will be declared if PF-06741086 prophylaxis reduces the ABR compared to ~~routine~~ on-demand treatment by at least 50%, ie, the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) is below 0.5. Participants with inhibitors who are on routine prophylaxis (defined as treatment by IV injection of bypass factor to prevent bleeding) may be allowed to enroll to supplement the safety evaluation of inhibitor cohort. The efficacy of these participants, if included, will be separately summarized using descriptive statistics without any hypothesis testing or inferential statistics. Non-Inhibitor Cohort ~~f~~For regions outside of the EU: to demonstrate ~~non-inferiority~~ superiority of PF-06741086 prophylaxis observed over ~~the~~ a 12-month Active Treatment Phase ~~compared~~ relative to ~~routine prophylaxis~~ on-demand treatment during the 6 months prior to receiving study intervention, on the ~~difference in~~ratio of the ABR of treated bleeds ~~(non-inferiority margin of 2.5)~~ using a repeated measures model to account for participant's experience in the OP and ATP, in participants ≥12 years of age with severe hemophilia A or moderately severe to severe hemophilia B (~~coagulation factor~~FVIII activity <1% or FIX activity ≤2%, respectively) ~~A or B~~ without inhibitors who receive ~~routine~~ on-demand treatment during the 6 months prior to receiving study intervention. Superiority will be declared if PF-06741086 prophylaxis reduces the ABR compared to ~~routine~~ on-demand treatment by at least 50%, ie, the two-sided 95% confidence interval of the ABR ratio estimate (PF-06741086 prophylaxis/on-demand treatment) is below 0.5. Note this is a secondary endpoint for the EU. ~~Non-Inhibitor Cohort for~~For the EU: to demonstrate non-inferiority of PF-06741086 prophylaxis observed over the 12-month Active Treatment Phase compared to routine prophylaxis during 6 months prior to receiving study intervention, on the difference in the ABR of treated bleeds (non-inferiority margin of 2.5) using a repeated measures model to account for participant's experience in the OP and ATP, in participants ≥12 years of age with severe hemophilia A or moderately severe to severe hemophilia B (~~coagulation factor~~FVIII activity <1% or FIX activity ≤2%, respectively) ~~A or B~~ without inhibitors who receive routine prophylaxis treatment during the 6 months prior to receiving study intervention.	participants with prior prophylaxis. To describe that analyses of data from participants with inhibitors with prior prophylaxis will be limited to separate descriptive summary without hypothesis testing.

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td></td><td>If non-inferiority is demonstrated on ABR, subsequent testing for superiority will be conducted on this endpoint. Note this is a secondary endpoint for regions outside the EU.</td><td></td></tr>
<tr><td>Section 9.2 Sample Size Determination</td><td>A sufficient number of participants will be screened to achieve ~~approximately~~ at least 145 participants dosed with PF-06741086. Of these, 45 participants will be dosed with PF-06741086 prophylaxis in the On-Demand Inhibitor Cohort; ~~approximately~~ at least 100 participants will be dosed in the Non-Inhibitor Cohort (with at least 67 of these participants receiving routine prophylaxis during the Observational Phase and at least 28 receiving on-demand during the Observational Phase). These 145 participants will ensure sufficient power for the primary endpoint (as described below) and also to achieve adequate assessment of safety in all cohorts. ~~Targeted o~~Over-enrollment by approximately 20~~10~~% (up to 174 participants) is planned to account for attrition of enrolled participants and to provide for sufficient representation into regions which have experienced recruitment delays due to the COVID-19 pandemic. ~~over the required number of evaluable participants in each cohort needed to provide sufficient power for the primary endpoint (as described below) is planned to ensure adequate assessment of efficacy; additionalfurther over enrollment is planned to achieve adequate assessment of safety in all cohorts.~~ Finally, participants with inhibitors receiving prior routine prophylaxis may also be allowed to enroll to supplement the safety evaluation of the inhibitor cohort; these participants will be included within this 20% over-enrollment group.</td><td>To align with the added allowance for additional participants in order to provide additional time for participants to be enrolled in countries which had difficulties enrolling due to the COVID pandemic and to allow for enrollment of participants with inhibitors receiving prior routine prophylaxis.

Wording changes aligned with updated inclusion criteria in participants with inhibitors with prior prophylaxis.</td></tr>
<tr><td>Section 9.3 Populations for Analyses</td><td><table><tr><th>Participant Analysis Set</th><th>Description</th></tr><tr><td>All Safety~~Enrolled~~</td><td>For inhibitors/non-inhibitors with prior prophylaxis in OP, all participants who received at least 1 prophylaxis or on-demand treatment at OP; for inhibitors/non-inhibitors with on-demand in OP, all participants who completed any of the procedures for Visit 2 (OP baseline). Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing will be excluded from this population. Participants who changed from an inhibitor to a non-inhibitor will be included in this population and considered as inhibitors in the analysis. Participants will be analyzed according</td></tr></table></td><td>All Safety: to achieve a less-biased safety comparison between treatments during the OP versus the ATP

All Safety and mITT: add handling of participants with change in inhibitor status during the study.

PF-06741086 Safety: to include</td></tr>
</table>

Section # and Name	Description of Change		Brief Rationale
		to the intervention they actually received. ~~All participants who sign the ICD and meet all eligibility criteria~~	all participants who received at least 1 dose of study drug.
	PF-06741086 Safety~~Evaluable~~	All participants who received at least 1 dose of PF-06741086 in ATP. ~~All participants enrolled in the study and entered OP and do not have any important protocol violation~~	
	mITT (modified Intent-to-Treat)~~All Safety~~	All participants who completed OP and received at least 1 dose of PF-06741086 in ATP. Participants who changed from a non-inhibitor to an inhibitor on or before ATP Day -7 testing will be excluded from mITT; participants who changed from an inhibitor to a non-inhibitor will be included in mITT and considered as inhibitors. This population will be utilized for all efficacy analyses. ~~For non-inhibitors with prior prophylaxis in OP, all participants who received at least one prophylaxis or on-demand treatment at OP; for inhibitors/non-Inhibitors with on-demand in OP, all participants who completed any of the procedures for visit 2 (OP baseline).Participants will be analyzed according to the intervention they actually received. Participants who do not maintain their cohort status will be excluded from All Safety Analysis Set.~~	
	~~PF-06741086 Safety~~	~~All participants who received at least one dose of PF-06741086 in ATP~~	
	Combined mITT Defined Analysis Set description with Participant Analysis Set table.		
Section 9.4.1 Efficacy Analyses	Mixed effects model with repeated measures (MMRM) analysis deleted and replaced with the Wilcoxon signed rank test.		Main analyses for all continuous variables were harmonized as the Wilcoxon signed rank test.
Section 9.5 Interim Analyses	Upon completion of the 12-month ATP for the Non-Inhibitor Cohorts (with prior on-demand therapy as well as with prior Prophylaxis), analyses of the primary endpoint of interest along with secondary endpoints in the corresponding participant populations may be performed to assess respective efficacy and safety for a potential initial registration filing regardless of whether or not		Final analyses for non-inhibitor cohorts: updated reflecting the most updated

Section # and Name	Description of Change	Brief Rationale
	follow-up is ongoing in the Inhibitor cohort. If conducted, these analyses will be considered the final analyses for these participant populations. The study will continue until the completion of participants from all cohorts. ~~Upon completion of follow-up for each of the participant populations (Inhibitor Cohort; Non-Inhibitor Cohort with prior On-Demand therapy; Non Inhibitor Cohort with prior Prophylaxis) analyses of the primary endpoint of interest along with secondary endpoints in the corresponding participant populations will be performed to assess respective efficacy and safety for a potential initial Biologic License Application filing and these analyses will be considered the final analyses for that participant population. Follow-up will continue in the remaining portion(s) of the study until such time that follow-up is completed.~~	recruitment projection.
Appendix 7: Country-Specific Requirements, Section 10.7.1 Japan Appendix; Section 10.7.3 China Appendix	Added text to Japan appendix describing blood collection/volume and added blood volume table for study sites located in Japan. Added appendix for study sites located in China, describing study population, study schema, and blood collection/volumes.	Updated lab sample volumes due to central laboratory vendor COVID-19 pandemic-related supply chain challenges. Laboratory analyses performed for study participants in Japan and China will differ in the specific blood volumes required for some of the protocol-specified laboratory tests. This is due to differences in minimum volume requirements for contracted laboratory facilities in closer proximity to Japan and China which will help to ensure timely and accurate analyses and result reporting from the

Section # and Name	Description of Change	Brief Rationale
		testing laboratories.

Amendment 5, 20 November 2020

The amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:
The protocol was amended based on feedback received by the Ministry of Food and Drug Safety (S. Korea) and the Polish regulatory authority to allow more flexibility to conduct safety assessments during the COVID-19 pandemic. Changes were made with regards to the estimated total blood volume and maximum allowed blood volume collection from the adolescent population based on the EMA guidance and following a request from the Italian Medicines Agency (AIFA) on this matter. Changes were also made to address feedback received from clinical study sites. Additional edits resulted from internal review to simplify protocol procedures, to clarify instructions, and to correct errors.

Text that has been deleted is shown with strikethrough and text that been added is shown as underlined.

Section # and Name	Description of Change	Brief Rationale
Header	Changed to 20 November 2020.	Changed to reflect the final Amendment 5.
Title page	Approval Date changed to 20 November 2020 and Amendment Number changed to 5.	Changed to reflect the final Amendment 5.
Synopsis, Tertiary/Exploratory Endpoints Section 3 Objectives, Estimands, and Endpoints	Analysis of changes in biomarkers: TFPI (total and free), peak thrombin ~~generation~~ [PKT], prothrombin fragment 1+2 [PF1+2], D-dimer, and dilute prothrombin time over duration of the study	Revised to correct protocol error.
Synopsis, Prior On-Demand Treatment	Individuals with inhibitors will receive on-demand treatment with recombinant factor VIIa (rFVIIa)<u>,</u> <u>Prothrombin Complex Concentrates (PCC),</u> or activated Prothrombin Complex Concentrates (aPCC) agents eg FEIBA or in regions where available, BYCLOT (Inhibitor Cohort) and individuals without inhibitors will receive on-demand	Prothrombin Complex Concentrates (PCC) added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the standard of care for treatment of inhibitor participants.

Section # and Name	Description of Change	Brief Rationale
	treatment with FVIII- or FIX-replacement therapy (Non-Inhibitor Cohort) during the Observational Phase before crossing over to the 12month Active Treatment Phase.	
Synopsis, Prior Prophylaxis Treatment	The anticipated study duration for an individual participant is approximately ~~20~~ 21 months, including an approximately ~~5-week~~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.	Overall study duration expanded since screening period increased.
Schema, Phase 3 Study Schematic Section 4.1 Overall Design, Figure 1 Phase 3 Study Schematic	Updated "Screening Period" from 5 weeks to 45 calendar days.	Screening duration increased to enable sites to have more flexibility in screening potential participants, in particular, when washing out participants from long-acting coagulation factor products.
Schedule of Activities, Observational Phase, Laboratory Notes	~~All laboratory tests will be performed at the central laboratory. In addition, FVIII or FIX inhibitor, FVIII or FIX activity, and cardiac troponin I (cTnI) (where available) assessments will also be performed at the local 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.	Factor activity analyses are permitted to be analyzed by either the central or local laboratory and factor inhibitor analyses are required to be performed at the central laboratory only, so as to provide flexibility for sites and to decrease the overall blood volume collected from adolescent participants.
Schedule of Activities, Observational Phase, FVIII or FIX Inhibitor Notes	~~At each timepoint FVIII or FIX inhibitor samples will be sent to both the local AND central laboratories.~~ At each timepoint, two aliquots will be collected for the central laboratory analysis to measure FVIII or FIX Inhibitor.	Factor inhibitor analyses are required to be performed at the central laboratory only, so as to provide flexibility for sites and to decrease the overall blood volume collected from adolescent participants.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities, Observational Phase, FVIII or FIX activity Notes	If documented historic FVIII or FIX activity <1% is not available then FVIII or FIX Activity bioanalysis will be ~~performed~~ analyzed by a clinical ~~the local AND central laboratories~~laboratory (either a local laboratory or the central laboratory used in this study). ~~Central laboratory activity results supersede the local laboratory results; central laboratory results are used to qualify the individual for the study.~~ ~~For participants with FVIII or FIX inhibitor (ie, participants in the Inhibitor Cohort), a FVIII/FIX recovery assessment will be conducted within 6 months prior to the Enrollment Visit.~~ 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 ~~so as to allow for~~ 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 ~~at any point throughout the study~~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).	Inclusion criteria modified to allow use of either a factor activity obtained during screening or a documented historic factor activity level from a clinical laboratory. This change was made based on site request to enable more flexibility in screening potential participants.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities, Observational Phase	Added row: Biomarker (Fibrinogen) Notes: 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. … Revised rows: Currently Prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT Discontinue prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT	Fibrinogen level (less than or equal to the lower limit of normal) is required prior to dosing at Visit 7. Since sample collection can be completed at any time from Visit 2 though Visit 7 (Pre-Dose), Fibrinogen was listed as its own row, to allow for flexibility in day of collection. PCC added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the standard of care for treatment of inhibitor participants.
Schedule of Activities, Observational Phase, ECG Notes	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~~. If the ECG is abnormal~~ (see Appendix 9 for examples of abnormalities)~~, then 2 additional ECGs will be interpreted by the ECG core laboratory.~~	Revised to correct protocol error.
Schedule of Activities, Observational Phase, Discontinue prescribed FVIII, FIX, rFVIIa, PCC, aPCC, or BYCLOT Notes	Discontinue scheduled use of FVIII, FIX, rFVIIa, aPCC, PCC, or BYCLOT prior to initiating study intervention in ATP Day 0.	Revised to correct protocol error.
Schedule of Activities, Observational Phase and Active Treatment Phase, Patient Report Outcomes (Questionnaires) Completion on site tablet Notes	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.	To clarify instructions for timing of health outcome-related questionnaires.
Schedule of Activities, Active Treatment Phase, Laboratory Notes	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	Factor activity analyses are permitted to be analyzed by either the central or local laboratory and factor inhibitor analyses are required to be performed at the central laboratory only so as to provide flexibility for sites and to

Section # and Name	Description of Change	Brief Rationale
	and central laboratories. All other laboratory tests will be analyzed at the central laboratory.	decrease the overall blood volume collected from adolescent participants.
Schedule of Activities, Active Treatment Phase, FVIII or FIX Inhibitor	Asterisk added to Active Treatment Phase Visit 20 (Day 360 Study Completion/Termination Visit) sample. Notes revised: FVIII or FIX Inhibitor bioanalysis will be ~~performed~~ analyzed by the ~~local AND~~ central laboratory~~ies~~. 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 ~~should~~ may use ~~the~~ a local lab result~~s~~ to progress the participants in the study. Two aliquots will be collected at each timepoint for ~~Central Laboratory~~central laboratory analysis. *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.	Factor inhibitor analyses are required to be performed at the central laboratory only so as to provide flexibility for sites and to decrease the overall blood volume collected from adolescent participants.
Schedule of Activities, Active Treatment Phase, FVIII or FIX activity	Asterisk added to Active Treatment Phase Visit 20 (Day 360 Study Completion/Termination Visit) sample. Notes revised: FVIII or FIX Activity bioanalysis will be analyzed ~~performed~~ by a ~~the~~ local laboratory ~~AND~~OR the central laboratory~~ies~~. … ~~Samples collected for ATP Day 180 and ATP Day 360 do not require a washout for prescribed factor replacement.~~ Two aliquots will be collected at each timepoint for ~~Central Laboratory~~central laboratory analysis. *This sample is collected from all adult participants; however, only collect this sample from adolescent	Factor activity analyses are permitted to be analyzed by either the central or local laboratory as to provide flexibility for sites and to decrease the overall blood volume collected from adolescent participants.

Section # and Name	Description of Change	Brief Rationale
	participants if their weight is >40 kg at Visit 20.	
Schedule of Activities, Active Treatment Phase, Hematology and Serum Chemistry (with lipid profile)	Moved sample from ATP Visit 7 (Day 0 Pre-Dose) to ATP Visit 6 (Day -7 Visit). Asterisk added to ATP Visit 18 (Day 300 Visit) sample. Added to Notes: *These samples are collected from all adult participants; however, only collect this sample from adolescent participants if their weight is >40 kg at Visit 18.	This change was made to decrease the overall blood volume collected from adolescent participants.
Schedule of Activities, Active Treatment Phase, Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level	Revised sample collection schedule to occur only after qualifying thrombotic event. Removed sample from ATP Visit 7 (Day 0 Pre-Dose). Revised Notes: 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.~~collected on Visit 7 (ATP Pre-dose) for later comparison, and only analyzed in the event a participant experiences a thrombotic event during participation in the Active Treatment Phase. If a thrombotic event occurs during the Active Treatment Phase, these samples will be collected at that time and a~~ All samples collected will be analyzed.	This change was made to decrease the overall blood volume collected from participants, adolescent participants in particular. These data are only required in the event of thrombosis after initiation of dosing with study drug; therefore, collecting at the Pre-Dose timepoint is not essential.
Schedule of Activities, Active Treatment Phase, Immunogenicity Tests and Serology Tests rows	Moved sample from ATP Visit 7 (Day 0 Pre-Dose) to ATP Visit 6 (Day -7 Visit).	This change was made to decrease the overall blood volume collected from participants, adolescent participants in particular. These data are required prior to dosing and moving the dose-relative timepoint from day of dosing to Day -7 has no impact.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities, Active Treatment Phase	Revised row: Biomarkers (TFPI, PF1+2, D-dimer, dPT, TGA) Asterisk added to ATP Visit 14 (Day 180 Visit) sample. Notes: Tissue factor pathway inhibitor (both Total TFPI and Free TFPI), prothrombin fragment 1+2, ~~fibrinogen,~~ 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. ~~The Day 0 Pre-Dose results for Fibrinogen 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.~~ *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. … Added row: Biomarker (Fibrinogen) Notes: The Day 0 Pre-Dose results for Fibrinogen 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. … Revised row:	This change was made to decrease the overall blood volume collected from adolescent participants. Fibrinogen level (less than or equal to the lower limit of normal) is required prior to dosing at Visit 7. Since sample collection can be completed at any time from Visit 2 though Visit 7 (Pre-Dose), fibrinogen was listed as its own row, to allow for flexibility in day of collection. Prothrombin Complex Concentrates (PCC) added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the

Section # and Name	Description of Change	Brief Rationale
	Currently prescribed FVIII, FIX, rFVII~~I~~a, PCC, aPCC, or BYCLOT for on-demand treatment only	standard of care for treatment of inhibitor participants.
Schedule of Activities, Active Treatment Phase, ECG Notes	Triplicate ECG 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~~. If the ECG is abnormal~~ (see Appendix 9 for examples of abnormalities)~~, then 2 additional ECGs will be interpreted.~~	Revised to correct protocol error, as ECGs are always collected in triplicate.
Section 2.3 Benefit/Risk Assessment	Added text: An additional risk of clinical trials, including Study B7841005, during the COVID-19 pandemic includes contact with other individuals while at or traveling to clinical trial sites. Appendix 13: Alternative Study Procedures During COVID-19 Pandemic, provides procedures to mitigate these risks for study participants during the COVID-19 outbreak.	Added additional risk concerning COVID-19 for participants based on feedback received by the Ministry of Food and Drug Safety (S. Korea) and the Polish RA.
Section 4.1 Overall Design	Note: The sponsor will provide PF-06741086 during the Active Treatment Phase of this study. Other medication for treatment of hemophilia (eg, factor-replacement products; bypassing agents) will not be provided. The expectation is that non-study hemophilia treatment products used by an individual participant will not change during the study. Any proposed changes to non-study hemophilia medication will require discussion and endorsement from the Pfizer Medical Monitor. Participants will need to obtain non-study drug through usual means. … Individuals with inhibitors will receive on-demand treatment with recombinant factor VIIa (rFVIIa), Prothrombin Complex Concentrates (PCC), or activated Prothrombin Complex Concentrates (aPCC) agents eg FEIBA or in regions where	To add further clarity based on site query. Prothrombin Complex Concentrates (PCC) added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the

Section # and Name	Description of Change	Brief Rationale
	available, BYCLOT (Inhibitor Cohort) and individuals without inhibitors will receive on-demand treatment with FVIII- or FIX-replacement therapy (Non-Inhibitor Cohort) during the Observational Phase before crossing over to the 12-month Active Treatment Phase. … The anticipated study duration for an individual participant is approximately ~~20~~21 months, including an approximately ~~5-week~~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.	standard of care for treatment of inhibitor participants. Screening duration increased to enable sites to have more flexibility in screening participants, in particular when washing out participants from long-acting coagulation factor products. This change also resulted in overall study duration now being closer to approximately 21 months.
Section 5.1 Inclusion Criteria, Age Section 6.6 Dose Modification	1. Participant must be male and 12 to <75 years of age with a minimum body weight of ~~30~~ 35 kg at the time of signing the informed consent. … The participant must weigh at least 50 kg in order to escalate to the 300 mg SC QW dose. Adolescent participants between ~~30~~ 35 kg and <50 kg (or any age participant <50 kg) must remain on the 150 mg dose.	Increased weight to 35 kg in order to minimize risk of collecting >1% of estimated total blood volume in pediatric patients (following EMA guidelines, estimating total blood volume in pediatric patients using approximately 80-90 mL/kg). Please note that the 50 kg limit for dose escalation was already in a prior version of the protocol. The ONLY change in this amendment is the increase of the minimum weight to 35 kg for adolescents and this rationale is the same as the rationale for the change listed above.
Section 5.1 Inclusion Criteria, Type of Participant and Disease Characteristics	2. Participants with a diagnosis of severe hemophilia A or B (FVIII or FIX activity <1%, respectively) documented by a 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	Inclusion criteria modified to allow use of either a factor activity obtained during screening or a documented historic factor activity level from a clinical laboratory. This change was made based on site request to enable more flexibility in screening participants.

Section # and Name	Description of Change	Brief Rationale
	laboratory for this study) prior to Enrollment.	
Section 5.2 Exclusion Criteria, Prior/Concomitant Therapy	9. Current routine prophylaxis with bypassing agent (eg, aPCC, BYCLOT, Prothrombin Complex Concentrates [PCC], or rFVIIa) ~~or,~~ non-coagulation non-factor replacement therapy (eg, emicizumab), or any previous treatment with a gene therapy product for treatment of hemophilia. • Potential participants who have previously received investigational non-factor-based hemophilia therapy (eg, fitusiran) will be considered on a case-by-case basis, only after discussion and agreement between the investigator and the Pfizer Medical Monitor.	Added exclusion for any previous treatment with a gene therapy product for treatment of hemophilia.
Section 6.1 Study Intervention(s) Administered	b. Administration of PF-06741086 by SC injection to the anterior thigh, backside of upper arm, and abdomen. Participants should rotate injection sites. ~~Other locations are acceptable if required.~~ If an arm is used for the SC injection, the opposite arm should be used for the PK/PD blood sample collections, if possible. Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection dose). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided.	Only the listed locations are to be used for injection of study drug; therefore, "other locations" was removed as an option. The listed locations are consistent with locations allowed in other studies on PF-06741086.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	For any participant who does not have a qualifying Factor VIII or Factor IX Activity laboratory report from a clinical laboratory prior to Screening, a Factor VIII or Factor IX Activity sample will be collected prior to Enrollment and after sufficient washout has been completed. In these cases, a washout from current hemophilia product will be required ~~Prior~~ prior to collection of factor activity on Day 1 (in the	Revised to provide additional clarity.

Section # and Name	Description of Change	Brief Rationale
	Observational Phase), ~~participants are required to adhere to a required washout period from their hemostatic products~~ as follows: … • from bypass agent therapy from either rFVIIa, PCC, aPCC, or BYCLOT for at least 72 hours. … The expectation is that non-study hemophilia treatment products used by an individual participant will not change during the study. Any proposed changes to non-study hemophilia medication will require discussion and endorsement from the Pfizer Medical Monitor in order for the participant to initiate dosing with study intervention.	Prothrombin Complex Concentrates (PCC) added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the standard of care for treatment of inhibitor participants.
Section 6.5.1 Permitted Hemostatic Medication, Table 1 Permitted Hemostatic Medication	Added to Inhibitor Row, Allowed During Observational Phase: rFVIIa, PCC, aPCC including FEIBA, or BYCLOT On-Demand, or preventative[d] only Added to Inhibitor Row, Allowed During Active Treatment Phase: **PF-06741086 Prophylaxis**[b,c] Breakthrough bleeding: • rFVIIa (≤90 µg/kg approx. every 2 hours), • or FEIBA at the lowest effective dose, in accordance with the Product Prescribing Information, but should not exceed 100 units per kg per 24 hrs, • or treatment with BYCLOT (in regions where available), in accordance with approved product labeling may be allowed per the specifications in Section 6.5.3 Treatment of Breakthrough Bleeding,	Prothrombin Complex Concentrates (PCC) added to expand flexibility to enroll participants in countries where rFVIIa or aPCC are not the standard of care for treatment of inhibitor participants. Restructured text to provide more clarity. PCC use added as noted previously.

Section # and Name	Description of Change	Brief Rationale
	• or aPCC or PCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information. … Added to footnote: - From bypass agent therapy (either rFVIIa, PCC, aPCC, FEIBA, or BYCLOT) for at least 72 hours.	PCC use added as noted previously.
Section 6.5.2.1 Observation and Active Treatment Phases	The following are prohibited throughout all phases of the study: immunomodulatory medications (eg, IVIG, routine systemic corticosteroids, rituximab) ~~and PCC~~and emicizumab.	PCC removed as a prohibited medication as now allowed. Clarification added to indicate that emicizumab is not permitted in either the Observational or Active Phase of the study.
Section 6.5.2.2 Active Treatment Phase	The following therapies are prohibited during the Active Treatment Phase unless required for the emergency management of acute breakthrough bleeds in the opinion of the investigator or ~~delegated~~ treating physician. • Non-Inhibitor Cohort: Prophylaxis treatment with FVIII- or FIX-replacement, or any use of~~emicizumab, and~~ bypassing agent therapy~~, in accordance with approved product labeling~~ (rFVIIa, PCC, aPCC, or BYCLOT) • Inhibitor Cohort: Prophylaxis, on-demand, or preventative treatment with FVIII- or FIX-replacement. Prophylaxis treatment with bypassing agent therapy (rFVIIa, PCC, aPCC, or BYCLOT).~~Bypass agent therapy with rFVIIa, aPCC products or emicizumab, in accordance with approved product labeling (eg, in regions where available, BYCLOT)~~	As noted above, emicizumab is not permitted in either the Observational or Active Phase of the study, so redundant to note again in the Active Phase sections.
Section 6.5.3 Treatment of Breakthrough Bleeding	An inhibitor participant should be stabilized utilizing rFVIIa bypass	As noted previously, PCC use is now allowed in the study. Also

Section # and Name	Description of Change	Brief Rationale
	agent therapy or PCC, aPCC, FEIBA, as follows: • For non-inhibitor participants who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or ~~delegated~~ treating physician requires additional hemostatic therapy beyond PF-06741086 prophylaxis, FVIII- or FIX-replacement products may be administered at the lowest effective dose and according to the approved product labeling. • For **inhibitor participants** who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or ~~delegated~~ treating physician requires additional hemostatic therapy beyond PF-06741086 prophylaxis, rFVIIa, PCC, aPCC, FEIBA, or BYCLOT (in regions where available) are allowable. o FEIBA may be administered at the lowest effective dose, in accordance with the Product Prescribing Information but should not exceed 100 units per kg per 24 hours. o PCC may be administered at the lowest effective dose, in accordance with the Product Prescribing Information. o aPCC may be administered at the lowest effective dose, in accordance with the	updated to add more clarification regarding aPCC use.

Section # and Name	Description of Change	Brief Rationale
	Product Prescribing Information.	
Section 6.7 Intervention After the End of the Study	An ~~12-month~~ extension study (B7841007) to assess safety is available for participants who complete the B7841005 study.	The extension study will continue until commercial availability, and the product available in the country, thus duration of the study will be variable by country.
Section 7.2 Participant Discontinuation/Withdrawal From the Study	~~Withdrawn due to Substantial Prophylaxis Regimen Change (for participants outside the US and Canada)~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Section 8 Study Assessments and Procedures Section 11 References	The maximum planned amount of blood collected from each adult participant over the duration of the study should not exceed ~~388.6~~320.4 mL and the maximum planned amount of blood collected from each adolescent participant over the duration of the study should not exceed 261.5 mL (based on Screening through Active Treatment Phase Visit 20). Table 2 reflects approximate sample volumes (for adults and adolescents) needed for each measured endpoint. Added text: Estimated total blood volume and maximum allowed blood volume collection from the adolescent participant population in this study is based on EMA Guidance entitled, "Ethical considerations for clinical trials on medicinal products conducted with minors."[19] These guidelines direct that total blood volume is estimated as approximately 80 mL/kg – 90 mL/kg. In this study, approximately 90 mL/kg is used as the estimated blood volume in adolescent participants. General criteria (from EMA) for safe blood volume collection in adolescent participants suggests limiting blood draws during a 24-hour period to 1% of total estimated blood volume and limiting blood draws during a 4-week period to 3% of total estimated blood	Revisions to sample collection schedule and individual sample volumes changed the total amount of blood planned for collection during participation. Per request from the Italian Medicines Agency (AIFA), limitations on blood volumes collected were implemented and new text added to provide guidance to minimize safety issues related to blood volume collection in adolescents.

Section # and Name	Description of Change	Brief Rationale
	volume. The blood volumes collected from adolescent participants during their participation in this study comply with this EMA Guideline. Where possible, adolescent participant samples should be collected using microtainer devices. Best practices for pediatric blood collection are included in Appendix 2: Clinical Laboratory Tests. … Reference added to Section 11: European Medicines Agency. Ethical Considerations for Clinical Trials on Medicinal Products Conducted With Minors. Recommendations of the Expert Group on Clinical Trials for the Implementation of Regulation (EU) No 536/2014 on Clinical Trials on Medicinal Products for Human Use. 18 September 2017.	
Section 8 Study Assessments and Procedures, Table 2 Approximate Blood Volume	Added separate columns for "Adult Blood Sample Volume (mL)" and "Adolescent Blood Sample Volume (mL)", and "Adult Total Volume (mL)" and "Adolescent Total Volume (mL)". Updated blood volumes to reflect separate columns. FVIII or FIX inhibitor and activity Rows: Revised wording in Adult Blood Sample Volume and Adolescent Blood Sample Volume columns: (~~4.5 local lab; 4.5 central lab~~includes back-up aliquot for central laboratory) FVIII or FIX activity Row: Removed sample from "Screening" and revised Total Volume (mL) …	This change was made to decrease the overall blood volume collected from participants, adolescent participants in particular. Separate blood volumes are being implanted for adult participants and pediatric participants so these details are provided for clarity. FVIII or FIX activity must be assessed to determine eligibility (when no historical factor activity is available to qualify participant) but is not collected at 2 timepoints. The "X" was removed from Screening and retained under Enrollment, for those participants who require analysis of this sample to determine eligibility. Central laboratory updated the sample volumes required and this

Section # and Name	Description of Change	Brief Rationale
	Revised Adult Blood Volume HIV row: Sample Volume ~~5~~ 2.5 Total Volume (mL): ~~10~~ 5	was changed accordingly in the protocol.
	… Added note to aPTT, PT/International Normalized Ratio (INR) row: *Note: Fibrinogen can also be analyzed from this tube when collected at the same timepoint.*	This note was added to allow sites to reduce the blood volume collected at a timepoint when Fibrinogen samples will also be collected at the same timepoint.
	… Added note to Fibrinogen row: *Note: aPTT and PT/INR can also be analyzed from this tube when collected at the same timepoint.*	This note was added to allow sites to reduce the blood volume collected at a timepoint when aPTT and PT/INR samples will also be collected at the same timepoint.
	… TFPI (both total and free), Dilute prothrombin time, and Thrombin generation assay rows: Number of Sampling Times Active Phase column revised to 7	
	… Added note to Prothrombin Fragment 1+2 and D-dimer row: *Note: Anti-thrombin III can also be analyzed from this tube when collected at the same timepoint.*	This note was added to allow sites to reduce the blood volume collected at a timepoint when anti-thrombin III samples will also be collected at the same timepoint.
	… Revised row: Other ~~Screening~~Tests (only collected from participants who experience a clinically significant AE for thrombosis during ATP): …	These tests are not performed during Screening.

Section # and Name	Description of Change	Brief Rationale
	Added note to Anti-thrombin III row: *Note: Prothrombin Fragment 1+2 and D-dimer can also be analyzed from this tube when collected at the same timepoint.* Revised Adult Blood Sample and Total Volumes Anti-thrombin III row: Adult Blood Sample Volume (mL): ~~1.8~~ 2.7 Adult Total Volume (mL): ~~1.8~~ … Anti-thrombin III, Factor V Leiden mutation, Prothrombin 20210 mutation, Protein C activity, and protein S level rows: Number of Sampling Times Active Phase removed … Moved "Prothrombin 20210 mutation" from Factor V Leiden mutation row to separate row. … Revised Total planned blood volume ~~for central OR local laboratory,~~ Adult Total Volume (mL): ~~388.6~~ 320.4, and Adolescent Total Volume (mL): 261.5	This note was added to allow sites to reduce the blood volume collected at a timepoint when Prothrombin Fragment 1+2 and D-dimer samples will also be collected at the same timepoint.
Section 8.1.7.4 Patient Reported Outcomes (PROs) Assessments	Observational Phase (OP) Baseline (Visit 2), ATP Visits 6, 7, 10, 12, 14, 16, and 20 (end of treatment or early termination).	Revised to add more clarity.
Section 8.3.3 Follow-up of AEs and SAEs	Assays for thrombophilic disorders (Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, and protein S level) ~~are collected at Visit 7, Pre-Dose during the ATP and~~ should only be collected ~~again~~ in the event that a participant experiences a thrombotic event at any time during	To provide additional clarity regarding the collection of these samples.

Section # and Name	Description of Change	Brief Rationale
	the Active Treatment Phase. ~~The Visit 7, Pre-Dose samples and~~All samples collected at the time of a thrombotic event will ~~then~~ be analyzed.	
Section 8.5 Pharmacokinetics	Blood samples of approximately 4.5 mL~~, to provide approximately 2 mL plasma,~~ will be collected into appropriately labeled tubes containing sodium citrate for measurement of plasma concentrations of PF-06741086 as specified in the SoA.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual.
Section 8.6.1 Tissue Factor Pathway Inhibitor	Blood samples of approximately 2.7 mL (combined for both total and free TFPI), at each timepoint~~, to provide approximately 1.4 mL plasma,~~ will be collected into appropriately labeled tubes containing sodium citrate for TFPI (total and free) analysis as specified in the SoA.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual.
Section 8.6.2 Thrombin Generation Assay	Blood samples of approximately 2.7 mL~~, to provide approximately 1.0 mL plasma,~~ will be collected into appropriately labeled tubes containing sodium citrate for the thrombin generation assay analysis as specified in the SoA.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual.
Section 8.6.3 Prothrombin Fragment 1 and 2 and D-dimer	Blood samples of approximately 2.7 mL (combined for Prothrombin Fragment 1+2 and D-dimer) will be collected into appropriately labeled tubes containing sodium citrate ~~to provide approximately 300 µL plasma~~ for PF1+2 and D-dimer analysis, ~~approximately 1.0 mL for coagulation tests analyses (D-dimer along with the following safety laboratories: fibrinogen, PT/INR, activated partial thromboplastin time (aPTT), protein C, and protein S), and remaining up to approximately 1.0 mL for back-up~~ as specified in the SoA.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual.

Section # and Name	Description of Change	Brief Rationale
Section 8.6.4 Dilute Prothrombin Time	Blood samples of approximately 4.5 mL~~, to provide approximately 1.4 mL plasma,~~ will be collected into appropriately labeled tubes containing sodium citrate for the dilute prothrombin time analysis as specified in the SoA.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual.
Section 8.7.1 Specified Genetics	Two blood samples of 2 mL each (4 mL in total) will be collected for DNA isolation, ONLY at the time a participant experiences a clinically significant AE of thrombosis at any time after initiating dosing with study intervention during the Active Treatment Phase. DNA samples will be analyzed for the purpose of assessing Factor V Leiden mutation and prothrombin 20210 mutation. No other genetic assessments are conducted.~~Genetics (specified analyses) are not evaluated in this study.~~	Revised to add more clarity and to include revised total blood volume collected from 2 mL to 4 mL, as modified by the analytical laboratory. These samples are no longer collected at a scheduled timepoint and are now only collected in the event of a clinically significant AE of thrombosis.
Section 8.8 Biomarkers	The following samples are required and will be collected from all participants in this study as specified in the SoA~~:~~. ~~ADAs (Anti-PF-06741086) and NAbs~~	Revised for clarity.
Section 8.8.1 Analysis of Anti-Drug Antibodies and Neutralizing Antibodies to PF-06741086	Blood samples of approximately 9.0 mL (4.5 mL sample for anti-drug antibodies; and a 4.5 mL sample for neutralizing antibodies)~~, to provide approximately 3.0 mL plasma,~~ will be collected for determination of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) to PF-06741086 as specified in the SoA (see Immunogenicity Tests in ATP) prior to administration of study intervention (at Visit 6). Thereafter, collection of ADA and NAb samples at subsequent visits during the Active Treatment Phase can be collected without regard to relative time from previous dose or next dose with study intervention.	Removed resulting plasma volumes, as this level of detail is provided in the Laboratory Manual, and revised to provide additional clarity.
Appendix 2 Clinical Laboratory Tests	The tests detailed in Table 4 will be ~~performed~~ analyzed by the central laboratory. In addition, FVIII	Revised to provide additional clarity.

Section # and Name	Description of Change	Brief Rationale
	activity~~,~~ and ~~FVIII inhibitor,~~ FIX activity may be analyzed at a local laboratory instead of the central laboratory. ~~, FIX inhibitor, and~~ Samples for cTnI (where available) assessments will also be ~~performed~~ analyzed at the local AND central laboratories~~y~~ at each timepoint. Added text: For adolescent participants, the following "Best Practices" for pediatric blood collection include: 1. Instruct parents to ensure child is well-hydrated prior to blood collection. 2. Keep the child warm throughout the process of preparing for and drawing blood. 3. Consider warming the area of the venipuncture site with a heat pack or warm cloth. 4. A lidocaine-based topical anesthetic (eg, lidocaine 4% cream) may be used prior to blood collection to decrease potential discomfort to the participant. The anesthetic must not contain propylene glycol. The skin must be thoroughly cleansed prior to blood sample collection. It is recommended that 2 venipuncture sites be prepared with local anesthetic in case the first attempt is not successful. 5. Use appropriate needle gauge for size of participant.	Per request from the Italian Medicines Agency (AIFA), new text added to provide guidance to minimize safety issues related to blood volume collection in adolescents.
Appendix 2 Clinical Laboratory Tests, Table 4 Protocol-Required Safety Laboratory Assessments	Revised Row: Other ~~Screening~~ Tests • Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, and protein S level (only collected and analyzed if participant experiences a thrombotic event during participation in the Active Treatment Phase). Factor V Leiden mutation and prothrombin 20210 mutation are genetic mutation tests which are	Revised per PACL to add more clarity and removed specification that these are "Screening" tests.

Section # and Name	Description of Change	Brief Rationale
	specific to the risk of thrombosis; no other genetic assessments are conducted. Revised footnote: The results of each test ~~performed~~ analyzed at the local laboratory must be entered into the CRF.	
Appendix 3 Section 10.3.3 Recording/Reporting and Follow-Up of AE or SAE, Assessment of Intensity	The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories using the CTCAE Version 5.0:	Revised to provide additional clarity.
Appendix 9 Section 10.9 ECG Findings of Potential Clinical Concern	Added below "ECG Findings That May Qualify as Adverse Events (AEs)": • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. Revised wording below "ECG Findings That May Qualify as Serious Adverse Events (SAEs): • Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (heart rate 40~~< x~~ bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (heart rate >100 bpm~~(~~, such as torsades de pointes).	To comply with the updated Pfizer protocol template.
Appendix 13 Section 10.13 Alternative Study Procedures During COVID-19 Pandemic	Revised: In the event that an in-clinic or unscheduled study visit cannot be conducted after Active Treatment Phase (ATP) Day -7, study sites are permitted to defer the conduct of the procedures, listed below, to the home health/mobile phlebotomy services or local medical establishments, provided that local regulations permit: • All protocol required lab draws. • Weight and vital signs (eg, body temperature, BP, pulse rate, respiratory rate).	Added text to provide additional flexibility to conduct safety assessments at a non-study center when necessary based on feedback

Section # and Name	Description of Change	Brief Rationale
	• Patient-Reported Outcomes (PROs). • Investigational Medication Dispensing and Accountability. • Dose Escalation Assessment (starting Visit 14, ATP Day 180). • Physical exam/brief physical exam. • Electrocardiogram. In the event that an in-clinic visit cannot be completed due to the COVID-19 pandemic, it is understood that the procedures, like the ones listed below, may not be able to be performed. In such cases, you should document the reason for the missed test (eg, in-clinic visit missed due to COVID-19 restrictions) on the case report form. ~~• Physical exam/brief physical exam.~~ ~~• Electrocardiogram.~~ • Hemophilia Joint Health Score (HJHS). • Patient Reported Outcomes Questionnaires. Added: If the participant or caregiver has any concerns regarding his safety and an in-clinic or unscheduled study visit cannot be performed due to COVID-related issues then the participant should visit his primary care physician or local clinic for an evaluation and appropriate medical treatment. The participant or caregiver should request that the medical provider consult with the study PI regarding this medical visit so appropriate medical care can be coordinated in accordance with the participant's ongoing participation in this study, B7841005.	received by the S. Korea MFDS and the Polish RA.

Amendment 4, 08 June 2020

The amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU).

Overall Rationale for the Amendment:
The protocol was amended based on feedback received from Health Canada, Italian Medicines Agency (AIFA), Paul Ehrlich Institute (PEI), Germany and The Health Products Regulatory Authority (HPRA) Ireland. Additional edits resulted from internal review to simplify protocol procedures, correct errors, and include alternative study procedures information during the COVID-19 pandemic.

Text that has been deleted is shown with strikethrough and text that been added is shown as underlined.

Section # and Name	Description of Change	Brief Rationale
Header	Changed to 08 June 2020.	Changed to reflect the final Amendment 4.
Title page	Approval Date changed to 08 June 2020 and Amendment Number changed to 4.	Changed to reflect the final Amendment 4.
Synopsis, Tertiary/Exploratory Endpoints Section 3 Objectives, Estimands and Endpoints	Analysis of changes in biomarkers: TFPI (total and free), peak thrombin generation [PKT], prothrombin fragment 1+2 [PF1+2], D-dimer, and dilute prothrombin time over duration of the study	Corrected error, missing biomarker added.
Schedule of Activities	Added: Alternative study visit information pertaining to the COVID-19 pandemic is described in Appendix 13 (Section 10.13).	Reference was added to new appendix describing alternative study procedures during COVID-19 pandemic.
Schedule of Activities, Observational Phase	Visit 1 OP Day ~~-35~~-45 to -1	Changed to enable increased flexibility for sites and participants.
Schedule of Activities, Observational Phase	Revised in Notes: It is recommended that OP Phone Follow-Up (Visit 5)~~can~~ 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.	Clarification. Added recommendation for Visit 5 and Visit 6 to occur at the same time.
Schedule of Activities, Observational Phase,	Added:	Clarification added.

Section # and Name	Description of Change	Brief Rationale
Informed Consent	Minor participants must be reconsented if they reach the age of majority during the course of the study, in order to continue participating.	
Schedule of Activities, Observational Phase	Revised rows: Demography~~, Height~~ Height and Weight	Editorial change to ease readability of table.
Schedule of Activities, Observational Phase FVIII or FIX activity	Removed "X" under Visit 1, Screening. Revised in Notes: Central laboratory activity results supersede the local laboratory results; central laboratory results are used to qualify the individual for the study. For participants with FVIII or FIX inhibitor (ie, participants in the Inhibitor Cohort), a FVIII/FIX recovery assessment will be conducted within 6 months prior to the Enrollment Visit. Samples collected for the Baseline (Visit 2) visit should be obtained during the period between Visit 1 and Visit 2 so as to allow for 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 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 a FVIII or FIX replacement therapy, or bypass agent therapy~~at any point throughout the study, the participant is to be stabilized~~,~~ – utilizing this regimen and a new washout period should be initiated (Section 6.5.1).	Clarification added to enable better understanding of protocol intent.
Schedule of Activities, Observational Phase PT/INR	Added PT/INR row and row notes: The Day 0 Pre-Dose results (during Active Treatment Phase) are required prior to dosing, in order to determine	The rationale for these changes is to provide clarification that results for PT/INR are required prior to dosing (instead of obtaining these results

Section # and Name	Description of Change	Brief Rationale
	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.	during Screening for enrollment), in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0.
Schedule of Activities, Observational Phase ECG Notes	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. If the ECG is abnormal (see Appendix 9 for examples of abnormalities), then 2 additional ECGs will be interpreted by the ECG core laboratory.	Revised for clarity.
Schedule of Activities, Active Treatment Phase	ATP Visit 6 window changed from ±7 days to ±10 days.	Added flexibility for washouts for extended half-life products.
Schedule of Activities, Active Treatment Phase	Revised in Notes: 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. 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).	Added plan for resumption of trial participant's original treatment at the end of the study or possibility to enroll into B7841007 to address request made by HPRA (Ireland).
Schedule of Activities, Active Treatment Phase	Revised row: Height and Weight	Included measurements of height in patients every 6 months during the study based on feedback from AIFA (Italian regulatory authority).
Schedule of Activities, ATP FVIII or FIX activity Notes	Added the following text: 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	Clarification of sample time.

Section # and Name	Description of Change	Brief Rationale
	(eg, the washout period may be adjusted to 4 times of an individual's half-life).	
Schedule of Activities, ATP PT/INR	Added to row notes: 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.	The rationale for these changes is to provide clarification that results for PT/INR are required prior to dosing (instead of obtaining these results during Screening for enrollment), in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0.
Schedule of Activities, Active Treatment Phase	Revised row: Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level Added to row notes: If a thrombotic event occurs during the Active Treatment Phase, these samples will be collected at that time and all samples collected will be analyzed.	Correction of minor inconsistencies in listing of pharmacodynamic/biomarkers between several protocol sections. Also to harmonize with text in Section 8.3.3 Follow-up of AEs and SAEs and Section 10.2 Appendix 2 Clinical Laboratory Tests.
Schedule of Activities, Active Treatment Phase Fibrinogen, Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level, Biomarkers	Deleted fibrinogen row and added fibrinogen to biomarkers row. Deleted anti-thrombin III from biomarkers row and added to Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level row. Added to Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level row Notes: If a thrombotic event occurs during the Active Treatment Phase, these samples will be collected at that time and all samples collected will be analyzed.	Correction of minor inconsistencies in listing of pharmacodynamic/biomarkers between several protocol sections.
Schedule of Activities, Active Treatment Phase Biomarkers	Added to row notes: The Day 0 Pre-Dose results for **Fibrinogen** 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	The rationale for these changes is to provide clarification that results for Fibrinogen are required prior to dosing (instead of obtaining these results during Screening for enrollment), in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0.

Section # and Name	Description of Change	Brief Rationale
	through the Day 0 Pre-Dose (Visit 7 Pre-Dose) visit.	
Schedule of Activities, Active Treatment Phase Study intervention administered at study center and as needed Notes, Study intervention administered by participant/caregiver Notes	Added: 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 7). However, emicizumab or any experimental medication should not be taken during the study period (including safety follow-up period of 28-35 days).	Added plan for resumption of trial participant's original treatment at the end of the study for participants not continuing into Study B7841007 or not continuing treatment with study intervention to address request made by HPRA (Ireland). Regularly prescribed treatment can resume after completing Visit 20.
Schedule of Activities, Active Treatment Phase Currently prescribed FVIII, FIX, rFVIIIa, aPCC, or BYCLOT for on-demand treatment only	Removed "X" from Visit 21.	Corrected error as participants are either resuming hemostatic treatment as prescribed or continuing study intervention into B7841007 upon completion of Visit 20.
Schedule of Activities, Active Treatment Phase Serious and non-serious adverse event monitoring	Added "X" to Visit 6.	Corrected error.
Section 2.2 Background	~~and 1000 mg IV monthly (QM)~~	Corrected error.
Section 2.2 Background	Added: The results of in vitro and in vivo nonclinical combination pharmacology studies of PF-06741086 and rFVIIa or FEIBA support concomitant use of rFVIIa at a clinical dose of ≤90 µg/kg or FEIBA at the clinical dose of 100 U/kg in the event that a breakthrough bleeding episode occurs in a hemophilia patient with an inhibitor to FVIII or FIX.[6]	Added brief summary of in vitro and in vivo nonclinical combination pharmacology studies of PF-06741086 and FEIBA and PF-06741086 and rFVIIa.
Section 2.3 Benefit/Risk Assessment	**Potential Benefits** Potential benefits of study participation for participants with hemophilia A or B (with or without inhibitors) include effective prophylaxis with PF-06741086 on a weekly SC dosing schedule that substantially reduces the burden of care associated with prophylactic treatment, eliminates the need for frequent IV infusions, potentially	Expanded overall Benefit/Risk Assessment section of the protocol based on requests from AIFA (Italy), PEI (Germany) and Health Canada.

Section # and Name	Description of Change	Brief Rationale
	obviates the need for indwelling central venous catheters and reduces or eliminates acute treatment of bleeding episodes with FVIII or FIX (or bypass agents), thereby reducing the antigenic exposure to FVIII or FIX. **Potential Risks** Individuals may experience risks or discomforts at the anatomical site of SC injection with PF-06741086. Injection Site Reactions, which may include pain, swelling, bruising, induration, and hematoma, are considered adverse drug reactions for PF-06741086. Potential risks for treatment with PF-06741086 are thrombi or emboli. Depending on location and severity, thrombi or emboli may be life threatening or fatal. Because PF-06741086 is a fully human IgG1 with no endogenous counterpart, the anti-drug antibody response (ADA) is expected to primarily affect the PK, efficacy and/or measurement of PF-06741086. An additional potential immunogenicity risk is the ADA-induced hypersensitivity. Therefore, individuals with a diagnosis or history of thrombotic or ischemic disease (including myocardial infarction, deep venous thrombosis or pulmonary embolism), individuals with coronary artery disease and individuals with an allergy to hamster protein should be excluded from study participation. PF-06741086 is expected to have efficacy outweighing the risks in participants who are eligible for this study but will be varied based on a participant's prior hemostatic therapy. All study participants will share the same potential risks regardless of their prior hemostatic therapy, while participants on prior on-demand treatment will potentially realize a	

Section # and Name	Description of Change	Brief Rationale
	greater benefit due to the anticipated reduction in bleeds.	
Section 3 Objectives, Estimands and Endpoints Primary Endpoints And Secondary Endpoints Section 9.1 Estimands and Statistical Hypotheses Section 9.1.1 Estimands Section 9.2 Sample Size Determination Section 9.4.1 Efficacy Analyses Secondary Endpoint Section 9.5 Interim Analyses	• For the Inhibitor Cohort, Non-Inhibitor Cohort, and Non-Inhibitor Cohort for the EU removed: • ~~using within participant comparison~~. • For ~~the US, Canada, and all other~~ regions outside the European Union	The phrase "within-participant comparison" was replaced with "using a repeated measures model to account for participant's experience in the OP and ATP" where applicable, or removed where no longer applicable. The phrase "the US, Canada, and all regions outside EU" was streamlined as "regions outside the EU".
Section 4.1 Overall Design and Synopsis Table 1 Permitted Homeostatic Medication (Section 6.5.1)	Added "Eg FEIBA" Added "including FEIBA" for the Inhibitor row, OP at 6 months. Added FEIBA to the list of bypass agent therapy in the table footnotes.	Revised text to accommodate addition of FEIBA for on-demand use by inhibitor patients during the Observational Phase and by inhibitor patients for breakthrough bleeding during the Active Treatment Phase.
Section 5.1 Inclusion Criterion #1	Added minimum body weight 30 kg to Inclusion Criteria.	Addition of minimum body weight of 30 kg based on feedback AIFA (Italy), since dosing with PF-06741086 is not weight-based.
Section 5.1 Inclusion Criteria #3 and #4	Revised Inclusion Criterion 3: during the 6 months period prior to ~~Screening~~ Enrollment into Observational Phase and willing to continue to receive on demand treatment during the Observational Phase. Revised Inclusion Criterion 4: previous ~~30 days~~6 months prior to Enrollment into Observational Phase	Expanded time period to provide FVIII or FIX recovery <60% of expected from "within previous 30 days" to 6 months prior to Enrollment into Observational Phase. This change was made based on clinical team discussions to enable flexibility for sites and participants and enable enrollment.
Section 5.2 Exclusion Criteria	Added to Exclusion Criterion 4: e. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (see Appendix 10.2.1 for formulas used in eGFR calculation).	Added eGFR formulas (1 for adult, 1 for pediatric participants) to an appendix as per request from AIFA (Italy).
Section 5.2 Exclusion Criteria	Removed from Exclusion Criterion 5: ~~b. Fibrinogen level <LLN~~	The rationale for these changes is to provide clarification that results for Fibrinogen and Prothrombin Time (PT) are required prior to dosing

Section # and Name	Description of Change	Brief Rationale
	Removed Exclusion Criterion 6: ~~6. Abnormal coagulation activity as defined by the following laboratory results at Screening:~~ ~~a. Prothrombin time (PT) >1.25 × ULN.~~	(instead of obtaining these results during Screening for enrollment), in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0.
Section 5.2 Exclusion Criteria	Revised Exclusion Criterion 16: ~~Baseline~~Screening 12-lead ECG	Clarification to identify the precise visit rather than nonspecific classification of "baseline".
Section 6 Study Intervention	The initial 300 mg loading dose ~~and~~ will be documented ~~these administrations~~ on the CRF. This will not be duplicated in the participant's diary. All other scheduled doses will be recorded on the participant's diary.	Clarification for documentation of study intervention doses.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	All participants must meet the following criteria prior to dosing with study drug in ~~following completion of the Observational Phase before transitioning to~~ the Active Treatment Phase: Prior to dosing, confirmed fibrinogen level ≥LLN. Prior to dosing, confirmed prothrombin time (PT) ≤1.25 × ULN.	The rationale for these changes is to provide clarification that results for Fibrinogen and PT are required prior to dosing (instead of obtaining these results during Screening for enrollment), in order to determine eligibility to begin dosing in the Active Treatment Phase on Day 0.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Edited the Note: (eg, participants prescribed "prophylaxis 2 times per week" may not significantly change [at the discretion of the investigator and the Sponsor's Medical Monitor] to a different dose or dosing frequency for prophylaxis treatments during the Observational Phase). Participants who require significant increase in dose or dosing frequency will be withdrawn from the study, at the discretion of the investigator and the Sponsor's Medical Monitor.	Allowance to provide flexibility for dose changes during the Observational Phase.
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Participants in the Inhibitor Cohort must meet the following criteria: • Documentation of current high titer inhibitor (≥5 BU/mL) or current low titer inhibitor (<5 BU/mL) ~~refractory to FVIII or FIX replacement and with FVIII or FIX recovery <60% of expected at the time of enrollment into the~~	Changed to remove requirement for recovery assessment prior to dosing as this is only a requirement for inclusion. Also, added an allowance for any participant who no longer meets the criteria for the cohort (inhibitor or non-inhibitor) to which they are

Section # and Name	Description of Change	Brief Rationale
	~~Observational Phase and at the Day -7 Visit in the Active Treatment Phase~~. • Participants who have documented inhibitors while on factor-replacement therapy but who do not meet the quantitative inhibitor criteria described in the prior bullet at the time of Screening may be considered for eligibility on a case-by-case basis with previously documented approval from the Pfizer Medical Monitor. • Inhibitor participants qualifying on this basis will be expected to have documented recovery of levels of less than 60% following FVIII or FIX replacement within 6 months of study enrollment. ~~All participants meeting~~ If the above protocol-specified criteria ~~for transitioning~~ are met, participants are eligible to transition into the Active Treatment Phase. ~~that are noted above will receive SC prophylaxis treatment QW with PF-06741086~~ If an inhibitor laboratory result obtained from the ATP Visit 6 assessment is received after ~~completion of the Observational Phase~~ dosing with study intervention during Visit 7, the participant may continue participation in the ATP of the study based on the medical judgement of the investigator, following discussion with the Medical Monitor. All other ~~Any~~ participants who no longer meet~~s~~ the criteria for the cohort to which they are assigned at Baseline (Visit 2) during the Observational Phase will be discontinued from the study.	assigned during the Observational Phase as a result of inhibitor laboratory analysis obtained from the ATP Visit 6 assessment to remain eligible to continue in the study based on the mutual medical judgement of the investigator and the medical monitor. This change was made based on team discussion to put patients first so as not to "penalize participants" who completed the Observational Phase.
Section 6.5.1, Table 1 Permitted Hemostatic Medication Inhibitor Cohort	**PF-06741086 Prophylaxis[b,c]** Breakthrough bleeding: rFVIIa (≤90 µg/kg approx. every 2 hours) or FEIBA at the lowest effective dose, in accordance with the Product Prescribing Information but should not exceed 100 units per kg per 24 hrs.~~;~~	Revised text to accommodate addition of FEIBA for on-demand use by inhibitor patients during the Observational Phase and by inhibitor patients for breakthrough bleeding during the Active Treatment Phase. Previously only allowed in an emergent situation when there were no better options and with

Section # and Name	Description of Change	Brief Rationale
	Also refer to Prohibited Medications in Section 6.5.2	consultation with Pfizer medical monitor. This change is based on data from completed in vitro and in vivo nonclinical combination pharmacology of PF-06741086 and FEIBA.
Section 6.5.2.2 Active Treatment Phase	Inhibitor Cohort: Bypass agent therapy with rFVIIa, aPCC products or emicizumab, in accordance with approved product labeling (eg, ~~Factor Eight Inhibitor Bypassing Activity [FEIBA] and~~ in regions where available, BYCLOT)	Revised text to correct for an error and accommodate addition of FEIBA for breakthrough bleeding.
Section 6.5.3 Treatment of Breakthrough Bleeding	Revised: If a participant experiences an acute bleeding episode at any point throughout the study, the participant is to be stabilized. A non-inhibitor participant should be stabilized utilizing the participant's standard hemostatic treatment regimen, which may include FVIII or FIX-replacement therapy~~, or~~ . An inhibitor participant should be stabilized utilizing rFVIIa bypass agent therapy or aPCC, FEIBA, as follows: … • For **inhibitor participants** Added: FEIBA or BYCLOT (in regions where available) are allowable. • FEIBA may be administered at the lowest effective dose, in accordance with the Product Prescribing Information but should not exceed 100 units per kg per 24 hours. Revised: • Treatment with ~~aPCC (eg, FEIBA and in regions where available,~~ BYCLOT (in regions where available), • removed "aPCC"	Revised text to accommodate addition of FEIBA for breakthrough bleeding.
Section 6.6 Dose Modification	The participant must weigh at least 50 kg in order to escalate to the 300 mg SC QW dose. Adolescent participants between 30 kg and	Addition of minimum body weight of 50 kg added to dose escalation criteria (from 150 mg QW to 300 mg QW, when applicable)

Section # and Name	Description of Change	Brief Rationale
	<50 kg (or any age participant <50 kg) must remain on the 150 mg dose. … Inhibitor Cohort: Two or more spontaneous (atraumatic) bleeds (consisting of joint bleeds or significant soft tissue/muscle or other site bleeds) treated with infusion(s) of Novo seven FEIBA or in regions where available, BYCLOT over a 6-month period.	ensure that exposures in adolescents or small adults that exceed those tested and established to be safe and effective are not allowed.
Section 7.1 Discontinuation of Study Intervention	Participants not continuing on PF-06741086 following completion or pre-mature discontinuation from this study will be eligible to resume their pre-study factor-based hemostatic products or bypassing agent therapy immediately upon discontinuation of study intervention and while PF-06741086 concentrations are washing out. This approach is justified based on the safe and effective co-administration of PF-06741086 and factor or bypassing agents observed in the development program to date. Participants should not receive emicizumab or any investigational hemostatic products for at least 30 days after receiving the last dose of study intervention during participation in this study.	Added the following statement to Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal section "Participants should not receive emicizumab or any investigational hemostatic products for at least 30 days after receiving the last dose of study intervention during participation in this study." Additional changes, as described in earlier rationales, made to address request from HPRA (Ireland).
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Added: A child's dissent should be respected.	To comply with the updated protocol template.
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Added SoA OP Visit 5.	Added detail to note that participants discontinue from the study during their participation in the Observational Phase of the study will complete Visit 5 Early Termination visit, while participants terminating early will complete Visit 20.
Section 8 Study Assessments and Procedures	The maximum planned amount of blood collected from each participant over the duration of the study~~, including any extra assessments that may be required, will~~ should not exceed 388.6~~321.9~~ mL (based on Screening through Active Treatment	Clarification of total blood volume guidance.

Section # and Name	Description of Change	Brief Rationale
	Phase Visit 20). Table 2 reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change~~, but the total blood volume collected should not increase~~.	
Section 8 Study Assessments and Procedures, Table 2 Approximate Blood Volume	Updated table blood volumes. Added CD4 and HIV rows under "Safety Labs" and removed "(including CD4 count, if HIV positive)" from Serology row. Added Fibrinogen row under "Biomarkers". Added Anti-thrombin III row under "Other Screening" and removed Anti-thrombin III from Prothrombin Fragment 1+2 and D-dimer row.	Revised blood volumes to match updated central laboratory collection specifications.
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Removed: ~~Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.~~	Removed to correct for an error as it referred to a period not applicable for protocol.
Section 8.3.1.2 Recording Non-serious AEs and SAEs on the CRF	~~During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.~~All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF. The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.	To comply with the updated protocol template.
Section 8.3.3 Follow-up of AEs and SAEs	The investigator should ~~contact the Pfizer Medical Monitor to discuss the most appropriate way~~ follow the local standard of care to manage the occurrence of a thrombotic event or situations (eg, sepsis and trauma) in which there may be increased activation of coagulation. Assays for thrombophilic disorders	Addition of thrombophilic assay collection added to harmonize with text in SoA and Section 10.2 Appendix 2 Clinical Laboratory Tests.

Section # and Name	Description of Change	Brief Rationale
	(Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, and protein S level) are collected at Visit 7, Pre-Dose during the ATP and should be collected again in the event that a participant experiences a thrombotic event. The Visit 7, Pre-Dose samples and samples collected at the time of a thrombotic event will then be analyzed. Refer to Section 7.1 (Discontinuation of Study Intervention) for recommended action with study intervention. Further information on follow-up procedures is given in Appendix 3.	
Section 8.3.8 Adverse Events of Special Interest	Added: Section 8.3.8. Adverse Events of Special Interest Not applicable	To comply with the updated protocol template.
Section 8.3.10 Medication Errors	In the event of a medication dosing error, the sponsor should be notified ~~immediately~~within 24 hours.	To comply with the updated protocol template.
Section 8.4 Treatment of Overdose	Contact the Medical Monitor ~~immediately~~within 24 hours.	To comply with the updated protocol template.
Section 8.5 Pharmacokinetics	Blood samples of approximately 4.5 mL, to provide approximately 2~~1.5~~ mL plasma, will be collected into appropriately labeled tubes containing sodium citrate for measurement of plasma concentrations of PF-06741086 as specified in the SoA.	Revised blood volume to match updated central laboratory collection specifications.
Section 8.6 Pharmacodynamics	Blood samples will be collected for measurement of TFPI (total and free), thrombin generation, prothrombin fragment 1+2, D-dimer, and dilute prothrombin time (Section 8.6.1, Section 8.6.2, Section 8.6.3, and Section 8.6.4, respectively). Biomarker concentration data (TFPI [total and free], thrombin generation, ~~anti-thrombin III,~~ PF1+2, D-dimer, and dilute prothrombin time) will be summarized for all participants for each of the study days samples are collected.	Correction of minor inconsistencies in listing of pharmacodynamic/biomarkers between several protocol sections.

Section # and Name	Description of Change	Brief Rationale
Section 8.6.2 Thrombin Generation Assay	Revised section heading: Thrombin Generation Assay Reduced plasma volume from 1.8 mL to 1.0 mL.	Revised blood volumes to match updated central laboratory collection specifications.
Section 8.6.3 Prothrombin Fragment 1 and 2 and D-dimer	Blood samples of approximately 2.7 mL (combined for ~~Anti-Thrombin III,~~ Prothrombin Fragment 1+2~~,~~ and D-dimer) will be collected into appropriately labeled tubes containing sodium citrate to provide approximately 300 µL plasma for PF1+2 analysis, approximately 1.0 mL for coagulation tests analyses (D-dimer along with the following safety laboratories: fibrinogen, PT/INR, activated partial thromboplastin time (aPTT), protein C, and protein S~~, and anti-thrombin III~~), and remaining up to approximately 1.0 mL for back-up as specified in the SoA.	Revised to match updated central laboratory collection specifications.
Section 9.3 Populations for Analyses	Revised column: Participant Analysis Set~~Population~~ Removed Dosed and Non-dosed rows Revised descriptions: Evaluable All participants enrolled in the study and entered OP~~received study medication~~ and do not have any important protocol violation~~significant interruption of efficacy measurement~~ All Safety For non-inhibitors with prior prophylaxis in OP, all participants who received at least one prophylaxis or on-demand treatment at OP; for inhibitors/non-Inhibitors with on-demand in OP, all participants who completed any of the procedures for visit 2 (OP baseline). ~~All participants enrolled in the study and received IP (same as Dosed population).~~ Participants will be analyzed according to the intervention they actually received. Participants who do not maintain their cohort status will be excluded from All Safety Analysis Set.	Definition of Safety Set was updated as two safety sets of All Safety and PF-06741086 Safety to facilitate adequate safety comparison between the observational period and the active treatment period; mITT definition was updated accordingly reflecting the change in safety sets; all these updated definitions also include clarifications on data handling for participants whose inhibitor status has changed due the development or resolutions of an inhibitor.

Section # and Name	Description of Change	Brief Rationale
	Added row: PF-06741086 Safety All participants who received at least one dose of PF-06741086 in ATP Revised column: Defined ~~populations for~~ A~~a~~nalysis Set Revised description: mITT (modified Intent-to-Treat) All participants who ~~enrolled in the study and received IP, same as Dosed Population.~~ completed OP, maintained the cohort status, and received at least one dose of PF-06741086 in ATP. For participants whose PF-06741086 dose is increased per Section 6.6, all post-dose modification observations will be excluded. All data during the preventative medical/dental treatment (plus 72 hours) are also excluded. Removed Non-dosed row	
Appendix 1 Section 10.1.3 Informed Consent Process	Revised throughout: his~~/her~~ his ~~or her~~ added: (defined as a parent, guardian, or other legally authorized representative as defined by local standards) And Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.	Editorial changes as only males eligible to enroll. Per UK EC request.
Appendix 2 Section 10.2 Clinical Laboratory Tests	In addition, FVIII activity, FVIII inhibitor, FIX activity, FIX inhibitor, and cTnI (where available) assessments will also be performed at the local laboratory at each timepoint.	Added "at each timepoint" for additional clarity that samples for these tests are always sent to local and central laboratories.
Appendix 2 Section 10.2 Clinical Laboratory Tests, Table 4 Protocol-Required Safety Laboratory Assessments	Removed from Other Screening Tests and added to new row, Other Coagulation Tests: • ~~PT/INR, aPTT, fibrinogen,~~ FVIII activity, FVIII inhibitor, FIX activity, FIX inhibitor, lipid profile	The rationale for these changes is to provide clarification that results for Fibrinogen and PT are required prior to dosing (instead of obtaining these results during Screening for enrollment), in order to determine

Section # and Name	Description of Change	Brief Rationale
	… Additional tests (needed for Hy's Law): AST, ALT (repeat), total bilirubin (repeat), albumin (repeat), alkaline phosphatase (repeat), direct bilirubin, indirect bilirubin, creatine kinase, GGT~~, PT/INR~~	eligibility to begin dosing in the Active Treatment Phase on Day 0.
Appendix 2 Table 4 Protocol-Required Safety Laboratory Assessments, Other Screening Tests	Anti-thrombin III, Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, and protein S level (only analyzed if participant experiences a thrombotic event during participation in the Active Treatment Phase)	Text added to harmonize with text in SoA and Section 8.3.3 Follow-up of AEs and SAEs.
Appendix 2	Added Section 10.2.1 Central Laboratory.	Added eGFR formulas as per request of AIFA (Italy).
Appendix 3 Section 10.3.2 Definition of SAE, Other situations	Added: Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.	To comply with the updated protocol template.
Appendix 3 Section 10.3.3 Recording/Reporting and Follow-Up of AE or SAE, Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	Recorded on the CRF ~~None~~All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded. Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness All (And EDP supplemental form for EDP). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.	To comply with the updated protocol template.

Section # and Name	Description of Change	Brief Rationale
Appendix 6 Section 10.6.1 Definition of AE and ADE	This definition includes events related to the investigational medical device or comparator ~~and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices~~for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only.	To comply with the updated protocol template.
Appendix 6 Section 10.6.2 Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect	Added cross-reference to Appendix 7 definition of SADE for Japan.	To harmonize with PMDA guidance.
Appendix 6 Section 10.6.4 Recording/Reporting and Follow-up of AEs and/or SAEs and Device Deficiencies	Added Clinical Description of Severity (Grade 1-5) table.	Changed severity assessment from 3 point scale to 5 point scale to be consistent with adverse event severity assessments.
Appendix 7 Section 10.7.1 Japan Appendix	Added: A SADE is defined as an Incident associated with a device, and the Incident was such that, if it occurred again, might lead to death or a serious deterioration in health (see Section 10.6.2 for the definition of SADE).	To harmonize with PMDA guidance.
Appendix 7 Section 10.7.2 France Appendix	Added underlined text to Section 10.7.2: Section 10.1.4. Data Protection Additional text added: The study sponsor, Pfizer Inc., and the study doctor/hospital undertake to process your collected data in compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of the 27 April 2016 applicable on 25 May 2018 (GDPR) and the data protection laws of France.	This was added at the request of a French Ethics Committee, in order to clearly state the country-specific requirement for Data Protection.
Appendix 13, Section 10.13 Alternative Study Procedures During COVID-19 Pandemic	Added appendix.	New appendix was added describing alternative study procedures during COVID-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
Section 11 References	Deleted reference: ~~Oldenburg J, Levy GG. Emicizumab Prophylaxis in Hemophilia A with Inhibitors. N Engl J Med. 2017;377(22):2194-5.~~	Deleted a reference that was included in error in previous version of protocol.

Amendment 3, 12 March 2020

The amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:
Food and Drug Administration (FDA) and Health Canada had previously restricted enrollment of prophylaxis participants until further safety data could be provided for the Phase 2 program. These data have been provided and both Agencies have now agreed to move forward and remove the restrictions to enroll prior prophylaxis participants.

Text that has been deleted is shown with strikethrough and text that been added is shown as underlined.

Section # and Name	Description of Change	Brief Rationale
Header	Changed to 12 March 2020	Changed to reflect the final Amendment 3
Title page	Approval Date changed to 12 March 2020	Changed to reflect the final Amendment 3
Synopsis 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 ~~for participants outside the US and Canada. In the US and Canada only, participants who are prescribed an on-demand treatment regimen may be enrolled.~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Synopsis and Section 4.1 Overall Design Prior Prophylaxis Treatment	Participants ~~outside the US and Canada~~ 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.	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.

Section # and Name	Description of Change	Brief Rationale
	~~For investigator sites in the US and Canada only: Any participants receiving routine prophylaxis treatment with FVIII/FIX replacement will not be enrolled. Only participants who are prescribed an on-demand treatment regimen may be enrolled. See Appendix 7 for details.~~	
Inclusion Criteria 3	Participants ~~outside the US and Canada~~ receiving routine prophylaxis (defined as treatment by IV injection of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement, have demonstrated at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrollment, and willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the Observational Phase ~~(For investigator sites in the US and Canada only: See Appendix 7 for details).~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Section 6.1.1. Medical Devices	~~1. Instructions for medical device use as a prefilled syringe are provided in the Investigational Product Manual.~~ ~~2. Prefilled syringe medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 8.3.8).~~ 1. The manufactured medical device provided for use in this study is a prefilled syringe, filled with PF-06741086 (marstacimab). 2. Instructions for medical device use are provided in the IP manual. 3. All medical device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.8) and appropriately managed by the sponsor.	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Note: Participants ~~outside the US and Canada~~ who are prescribed a prophylaxis treatment regimen are permitted to administer prescribed On-Demand treatment of bleeding episodes as needed	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Table 1 Permitted Homeostatic Medication	~~(prophylaxis only allowed outside the US and Canada)~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Section 7.2. Participant Discontinuation/Withdrawal from the Study	~~• , or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.~~ • A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following: • Refused further follow-up; • Lost to follow-up; • Death; • Study terminated by sponsor; • At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA ATP Day 360 (Visit 20) for assessments ~~data~~ to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. • The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. • If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	records and notify the sponsor accordingly. • If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. • Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.	
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Withdrawn due to Substantial Prophylaxis Regimen Change ~~(for participants outside the US and Canada)~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Section 8.3. Adverse Events and Serious Adverse Events	Added the following text: The definitions of device-related safety events (ADEs and SADEs) can be found in Appendix 6. Device deficiencies are covered in Section 8.3.8.	Required change for all amendments as a result of the release of an updated protocol template
Section 8.3.8. Medical Device ~~Incidents~~ ~~(~~Deficiencies ~~Including Malfunctions)~~	Section heading change	Required change for all amendments as a result of the release of an updated protocol template
Section 8.3.8.1. Time Period for Detecting Medical Device ~~Incidents~~Deficiencies	• Medical device incidents or malfunctions of the device ~~that result in an incident~~ will be detected, documented, and reported during all periods of the study in which the medical device is used.	Required change for all amendments as a result of the release of an updated protocol template
Section 8.3.8.2. Follow-up of Medical Device ~~Incidents~~Deficiencies	Follow-up applies to all participants, including those who discontinue study intervention. ~~• All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue study intervention.~~ • New or updated information will be recorded on ~~the originally~~	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	~~completed form~~ a follow-up with all changes signed and dated by the investigator.	
Section 8.3.8.3. Prompt Reporting of Medical Device ~~Incidents~~ Deficiencies to Sponsor	• ~~Medical device incidents~~ Device deficiencies will be reported to the sponsor ~~within 24 hours~~ 1 day after the investigator determines that the event meets the protocol definition of a medical device ~~incident~~deficiency. Information will be provided to the sponsor as described in the IP Manual. Include if applicable: The Medical Device Complaint CRF will also be completed. • Any device deficiency that is associated with an SAE must be reported to Pfizer Safety within 24 hours upon the investigator's awareness as outlined in Sections 8.3.1.1 and 8.3.1.2. • The sponsor will be the contact for the receipt of device deficiency information. ~~• The Medical Device Incident Report Form will be sent to the sponsor by an electronic data collection tool. If this is unavailable, then a paper SAE tool should be utilized.~~ ~~• The same individual will be the contact for the receipt of medical device reports and SAE.~~	Required change for all amendments as a result of the release of an updated protocol template
Section 8.3.8.4. Regulatory Reporting Requirements for ~~Medical~~ Device ~~Incidents~~Deficiencies	• The investigator will promptly report all ~~incidents~~ device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.	Required change for all amendments as a result of the release of an updated protocol template
Section 9.1.1 Estimands	For the Inhibitor Cohort and for the Non-Inhibitor Cohort aiming for the US, Canada, and all other regions outside of the EU, the ratio of ABR is estimated for the PF-06741086 prophylaxis for the 12-month Active Treatment Phase during	Added for consistency with the language

Section # and Name	Description of Change	Brief Rationale
	Active Treatment Phase over the routine on-demand treatment during the Observational Phase.	
Section 9.2 Sample Size Determination	… in the Non-Inhibitor Cohort (with at least 67 of these participants, ~~all regions outside of the US and Canada~~, receiving routine prophylaxis during the Observational Phase and at least 28 receiving on-demand during the Observational Phase).	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.
Section 10.6 Appendix 6 Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow up, and Reporting ~~Medical Device Incidents: Definition and Procedures for recording, Evaluation, Follow up, and Reporting~~	Definitions of a Medical Device Incident The definitions and procedures detailed in this appendix are in accordance with ISO 14155. Both the investigator and the sponsor will comply with all local medical device reporting requirements.	Required change for all amendments as a result of the release of an updated protocol template
Section 10.6.1. Definition of AE and ADE	AE and ADE Definition ~~Medical Device Incident Definition~~ • An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. ~~A medical device incident is any malfunction or deterioration in the~~	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	~~characteristics or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.~~ • ~~Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.~~ Definitions of a Medical Device Incident The definitions and procedures detailed in this appendix are in accordance with ISO 14155. Both the investigator and the sponsor will comply with all local medical device reporting requirements. The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.	
Section 10.6.2 definition of AE and ADE	• An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices. • An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.	Required change for all amendments as a result of the release of an updated protocol template
Section 10.6.3. Definition of SAE, SADE, and	If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g.,	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
Unanticipated Serious Adverse Device Effect	hospitalization for signs/symptoms of the disease under study, death due to progression of disease). An SAE is an AE that: a. Led to death b. Led to serious deterioration in the health of the participant, that either resulted in: 1. A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, that hypothetically might have caused death, if it were more severe 2. A permanent impairment of a body structure or a body function, 3. Inpatient or prolonged hospitalization, Planned hospitalization for a preexisting condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE 4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c. Led to fetal distress, fetal death or a congenital abnormality or birth defect SADE Definition • A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. 1. USADE Definition • A USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis management file (see Section).	
Section 10.6.4. Definition of Device Deficiency	2. Device Deficiency Definition • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
Section 10.6.5. Recording/Reporting and Follow-up of AEs or SAEs and Device Deficiencies	AE, SAE and Device Deficiency Recording • When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the CRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of following the reporting process described in the IP Manual [if applicable: and completing the Medical Device Complaint CRF]. • There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident. o A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. Assessment of Intensity The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	• Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Assessment of Causality • The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the [IB or product information, for marketed products,] in his/her assessment. • For each AE/SAE/device deficiency, the investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event	

Section # and Name	Description of Change	Brief Rationale
	before the initial transmission of the SAE data to the sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements Assessment of Intensity The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. Assessment of Causality • The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event	

Section # and Name	Description of Change	Brief Rationale
	to study intervention administration will be considered and investigated. • The investigator will also consult the [IB or product information, for marketed products,] in his/her assessment. • For each AE/SAE/device deficiency, the investigator must document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements Follow-up of AE/SAE/device deficiency • The investigator is obligated to perform or arrange for the conduct of supplemental measurements or evaluations as medically indicated or as requested by the sponsor to elucidate the nature or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • [If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.] MAY NOT BE REQUIRED FOR STUDIES WHERE DEATH IS AN ENDPOINT. • New or updated information will be recorded in the originally completed CRF.	

Section # and Name	Description of Change	Brief Rationale
	• The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information	
Section 10.6.6. Reporting of SAEs	SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool • The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone. SAE Reporting to Pfizer Safety via CT SAE Report Form • Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.	Required change for all amendments as a result of the release of an updated protocol template
Section 10.6.6. Reporting of SAEs	SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool • The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as the data become available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone. SAE Reporting to Pfizer Safety via CT SAE Report Form • Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety. • In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.	
10.6.7. Reporting of SADEs	SADE Reporting to Pfizer Safety NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities	

Section # and Name	Description of Change	Brief Rationale
	and IRBs/ECs as required by national regulations.	
Section 10.6 Appendix 6	~~It is sufficient that:~~ ~~• An incident associated with a device happened.~~ ~~AND~~ ~~• The incident was such that, if it occurred again, might lead to death or a serious deterioration in health.~~ ~~A serious deterioration in state of health can include any of the following:~~ ~~• Life-threatening illness~~ ~~• Permanent impairment of body function or permanent damage to body structure~~ ~~• Condition necessitating medical or surgical intervention to prevent one of the above~~ ~~• Fetal distress, fetal death, or any congenital abnormality or birth defects~~ ~~Examples of Incidents~~ ~~• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.~~ ~~• A participant's study intervention is interrupted or compromised by a medical device failure.~~ ~~• A misdiagnosis due to medical device failure leads to inappropriate treatment.~~ ~~• A participant's health deteriorates due to medical device failure.~~ ~~Documenting Medical Device Incidents~~ ~~Medical Device Incident Documenting~~ ~~• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF.~~ ~~• For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 3.~~ ~~• The CRF will be completed as thoroughly as possible and signed by the~~	Required change for all amendments as a result of the release of an updated protocol template

Section # and Name	Description of Change	Brief Rationale
	~~investigator before transmittal to the sponsor or designee.~~ ~~• It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.~~ ~~• A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.~~	
Section 10.7 Appendix 7: Country-specific Requirements	~~For investigator sites in the US and Canada only:~~ ~~Any participants receiving routine prophylaxis treatment with FVIII/FIX replacement will not be enrolled.~~ ~~The Sponsor may amend the protocol to enroll participants receiving routine prophylaxis following approval from the FDA and Health Canada based on emerging efficacy and safety data from participants with an on-demand treatment regimen during the Observational Phase of the current study and participants in Phase 2 studies B7841002 and B7841003.~~ ~~Synopsis Section 1.1 and Section 4.1, Overall Design:~~ ~~Enrollment of individuals into the Observational Phase who are on prior on-demand or prophylaxis treatment will begin at the same time for participants outside the US and Canada. In the US and Canada only, participants who are prescribed an on-demand treatment regimen may be enrolled.~~ ~~Only participants with hemophilia A or B who receive on-demand treatment will be enrolled in the US and Canada.~~ ~~Section 5.1, Inclusion Criterion #3, second bullet:~~ ~~• Participants outside the US and Canada receiving routine prophylaxis (defined as treatment by IV injection of factor concentrate to prevent bleeding) treatment with FVIII/FIX replacement, have demonstrated at least 80% compliance with scheduled prophylaxis regimen during 6 months prior to enrollment,~~	As per FDA and Health communication, the restricted enrollment of prophylaxis participants from the US and Canada has been removed.

Section # and Name	Description of Change	Brief Rationale
	~~and willing to continue to receive routine prophylaxis treatment with FVIII/FIX replacement during the Observational Phase.~~ ~~This inclusion criterion is not applicable as participants with hemophilia A or B receiving routine prophylaxis in the US and Canada will not be enrolled.~~	

Amendment 2, 12 November 2019

The amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union (EU) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:
The protocol was amended based on Scientific Advice given in January 2019 by the Committee for Medicinal Products for Human Use (CHMP) and based on Input in October 2019 from the Japan Pharmaceuticals and Medical Devices Agency (PMDA).

Text that has been deleted is shown with strikethrough and text that been added is shown as underlined.

Section # and Name	Description of Change	Brief Rationale
Header	Changed to 30 October 2019	Changed to reflect the final Amendment 2
Title page	Added confidential statement as per the template	To be compliant with the template
Throughout	For prophylaxis treatment, added: "For the United States (US), Canada, and <u>all other regions outside of the EU</u>"	For the purposes of defining the primary endpoint, additional language was added.
Objectives and Endpoints Table	Added: <u>Safety Endpoints</u> <u>Type I error control would not be applied to the following safety endpoints:</u> And • <u>Incidence and severity of thrombotic microangiopathy</u> • <u>Disseminated intravascular coagulation/consumption coagulopathy</u>	Added per CHMP scientific advice

Section # and Name	Description of Change	Brief Rationale
Throughout	Added definition of adolescents	Clarification
Synopsis and Body	Added the generic name of PF-06741086, marstacimab.	Generic was provided and included in the protocol.
Synopsis, SoA OP/ATP, and Body (Section 4.1 Overall Design, Exclusion Criteria Prior and Con Meds, Table 1, Section 6.3 measures to minimize Bias, Section 6.5.2.2 ATP, Section 6.5.3 Treatment of Breakthrough Bleeding)	Added: or in regions where available, BYCLOT (Inhibitor Cohort) and or BYCLOT	Added to provide flexibility for Japanese sites. BYCLOT is an APCC approved in Japan.
Synopsis Intervention Groups and Duration page 27	**Prior Prophylaxis Treatment:** Participants outside the US and Canada 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. **For investigator sites in the US and Canada only:** Any participants receiving routine prophylaxis ~~(defined as treatment by intravenous injection of factor concentrate to prevent anticipated bleeding)~~ treatment with FVIII/FIX replacement will not be enrolled.	Clarification
Schedule of Activities, Observational Phase	Added to Visit 5 Phone Follow-Up/OP Completion/Early termination during OP	To collect in the Case Report Form (CRF) and be able to report for the population conclusion of phase or early termination by phase.
Schedule of Activities, Observational Phase	Removed columns: "~~washout period prior to factor activity on Day~~ 1" And "~~At least 3-4 days prior to Baseline~~"	Ease the burden on study participants by removing the washout requirement on Day 180 and Study completion
Schedule of Activities, Observational Phase	Visit 5 ~~Minimum~~ 180 (±14) days from Day 1	Added window to provide additional flexibility for participants and ensure compliance with visits' schedule.
Schedule of Activities, Observational Phase	Removed from Notes:	Various notes for activities were re-arranged for greater clarity

Section # and Name	Description of Change	Brief Rationale
	~~Duration of washout of participant's prior hemophilia treatment prior to factor activity assessments on Day 1 is dependent upon prior treatment as follows:~~ ~~• from FVIII replacement therapy for at least 72 hours,~~ ~~• from Extended Half-Life FVIII replacement therapy for at least 4× half-life~~ ~~• from FIX replacement therapy for at least 96 hours~~ ~~• from Extended Half-Life FIX replacement therapy for at least 4× half-life;~~ ~~• from bypass agent therapy from either rFVIIa or aPCC for at least 72 hours.~~ ~~If factor replacement or bypass agent therapy is required to treat a bleeding episode during this Washout Period, then the participant may return for the Active Treatment Phase Day 0 visit after completing the required washout period and remain eligible for study participation.~~	
Schedule of Activities, Observational Phase	Added "laboratory" row and the following notes: All laboratory tests will be performed at the central laboratory. In addition, FVIII or FIX inhibitor, FVIII or FIX activity, and cardiac troponin I (cTnI) (where available) assessments will also be performed at the local laboratory. Refer to Section 10.2 for details.	Various notes for activities were re-arranged for greater clarity
Schedule of Activities, Observational Phase FVIII or FIX Inhibitor Notes	Separated the notes for the FVIII or FIX Inhibitor and the FVIII or FIX Activity and replaced the old text with the current, as shown below: 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 will be used to determine eligibility for enrollment. At each timepoint FVIII or FIX inhibitor	Clarification

Section # and Name	Description of Change	Brief Rationale
	samples will be sent to both the local AND central laboratories. At each timepoint, two aliquots will be collected for the Central Laboratory analysis to measure FVIII or FIX Inhibitor.	Added a second aliquot for Inhibitor sample to ensure these critical data are available in the event of any unexpected issues related to sample processing and analysis.
Schedule of Activities, Observational Phase FVIII or FIX Activity Notes	Separated the notes for the FVIII or FIX Inhibitor and the FVIII or FIX Activity and replaced the old text with the current, as shown below: FVIII or FIX Activity bioanalysis will be performed by the local AND central laboratories. Samples collected at the Baseline (Visit 2) visit must be after minimum washout period completed for prescribed factor-replacement product. 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).	Clarification Added a second aliquot for inhibitor samples to ensure that these critical data are available in the event of any unexpected issues related to sample processing and analysis. Added clarifications regarding FVIII and FIX activity analyses and required washouts.
Schedule of Activities, OP, ECG and Section 8.2.3 Electrocardiograms	Added 2 ECG measurements to a total of 3 measurements at each timepoint for central interpretation.	Central Vendor will interpret – If abnormal, interpretation of additional 2 ECGs will be performed).
Schedule of Activities, Observational Phase	Added Cohort Assigned" row and notes: Participants are assigned to appropriate cohort, including "Hemophilia A or B", "Inhibitor or Non-Inhibitor", "Prophylaxis or On-Demand", "Adult or Adolescent".	Clarification to identify that enrollment will be tracked in real time, Cohort by Cohort in Pfizer's enrollment tracking system.
Schedule of Activities, Observational Phase Patient Reported Outcomes (Questionnaires) Completion on site tablet	Switched from Visit 3-4 to Baseline of Active Treatment Phase	To ease burden on participant the ePRO data will be collected Baseline at Active Treatment Phase and thereby we remove the requirement for participants to have to return after the Observation Phase
Schedule of Activities, Observational Phase eDiary Dispensed and Training and ATP eDiary Collected And Throughout	Note: ~~in the event the~~ until eDiary is ~~not~~available, a paper diary may be used ~~during~~ throughout the study Note: in the event the eDiary is not available, a paper diary may be	Added that paper Diary can be used throughout the study in the event electronic Diary (eDiary) availability is delayed in any region

Section # and Name	Description of Change	Brief Rationale
	used during the ~~Observational Phase for the initial visits~~study.	
Schedule of Activities, Active Treatment Phase	Added in Notes: During an Early Termination Visit (ATP Day 360, Visit 20) all attempts should be made to complete all assessments.	Clarification to ensure all assessments are completed for early termination participants.
Schedule of Activities, Active Treatment Phase FVIII or FIX Inhibitor Notes	~~Both~~FVIII or FIX Inhibitor ~~and activity~~ bioanalysis will be performed by the local AND central laboratories. ~~FVIII or FIX activity: Samples~~ 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 should use the local lab results to progress the participants in the study. Two aliquots will be collected ~~after minimum washout period completed~~ at each timepoint for ~~prescribed factor-replacement product~~ Central Laboratory analysis.	Clarification
Schedule of Activities, Active Treatment Phase Visit window	Increased visit window days from ±2 to ±7 for ATP Day -7 Visit 6	To provide adequate time and flexibility to complete the required inhibitor washout.
Schedule of Activities, Active Treatment Phase FVIII or FIX Activity Notes	FVIII or FIX Activity bioanalysis will be performed by the local AND central laboratories. FVIII or FIX activity: Samples collected at the Visit 7 (ATP **Pre**-Dose) Visit must be after the minimum washout period is completed for the prescribed factor-replacement product. 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). Samples collected for ATP Day 180 and ATP Day 360 do not require a washout for prescribed factor replacement. Two aliquots will be collected at each timepoint for Central Laboratory analysis.	Clarification added to provide details with regard to washout and sample collection with regard to FVIII and FIX activity.
Schedule of Activities, Active Treatment Phase PF-06741086 concentration Notes	Added 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	Clarification regarding sampling time of PK collection.

Section # and Name	Description of Change	Brief Rationale
	administration occurs. Dosing should not be delayed or withheld in the evens 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).	
Throughout	Added clarification that tissue factor pathway inhibitor (TFPI) samples were for both total and free TFPI.	Clarification
Schedule of Activities, Active Treatment Phase	Removed Registration in IVRS/IWRS	Central laboratory analysis of FVIII or FIX Inhibitor will be used for IVRS assignment only during Observational Phase. Based on discussion with IRT team the term "IVRS registration" was removed from ATP SoA.
Schedule of Activities, Active Treatment Phase, Study Intervention ~~administration observed~~ administered at study center and as needed	Notes: On Visit 7 (ATP **Post**-dose), study intervention will be administered by the site staff~~Additionally, doses may be administered at the study center on AP Day 7, AP Day 28,~~ and ~~AP Day 60, ideally~~ recorded in the CRF. All other doses will be administered by the participant~~or caregiver~~/caregiver and ~~observed by~~ documented in the ~~study staff~~ eDiary. Participant or caregiver will be retrained on study intervention administration, if required. ~~Study intervention may be administered by study staff when needed. Study intervention~~ For participants who come to the study center for dose administration ~~given by study staff will be recorded on the case report form and entries~~ on Days 7, 28, or 60, it is recommended that PK sample be obtained before dose administration occurs. Dosing should not ~~duplicated~~ be delayed or withheld in the ~~participant diary~~ event that the PK blood sample cannot be taken before dose administration. ~~All other doses~~ Study drug will be administered ~~at home.~~ once weekly (QW). See Section 6.4 for details if participant misses a scheduled dose.	Multiple clarifications regarding protocol specifications of dosing administered by site staff vs participant or caregiver.
Schedule of Activities, Active Treatment Phase,	Added Visits 8,9, and 10 and notes:	Clarification

Section # and Name	Description of Change	Brief Rationale
Study intervention ~~administration at home~~ administered by participant/caregiver	Doses administered by the participant/caregiver may be administered by the study center, as needed. Study drug will be administered once weekly (QW).	
Schedule of Activities, Active Treatment Phase	Added Medication Error Row with Visits 7 (post dose) through 20	Clarification
Schedule of Activities, Active Treatment Phase	Added Currently prescribed FVIII, FIX, rFVIIIa, aPCC, or BYCLOT for on-demand treatment only Row with Visits 6 through 21 Notes: Use of these medications will be recorded in the participant's diary.	Clarification
Schedule of Activities, Active Treatment Phase eDiary row	Notes: Bleed, non-study drug infusions, and ~~infusion log~~ study drug injections entries, as applicable.	Clarification
Section 2.2 Background	Changed paragraph 6 and 7	Reflects completion of Study B7841002
Schedule of Activities, Active Treatment Phase, Dose Escalation Assessment	Changed from "will increase" to "may increase"	Added to clarify this is not a mandatory step.
3 Objectives Estimands and Endpoints	Added 2 bullets under the primary endpoints • Incidence and severity of thrombotic microangiopathy • Disseminated intravascular coagulation/consumption coagulopathy	Scientific Advice given in January 2019 by CHMP.
4.1 Overall Design	Added a note Note: The sponsor will provide PF-06741086 during the Active Treatment Phase of this study. Other medication for treatment of hemophilia (eg, factor-replacement products; bypassing agents) will not be provided. Participants will need to obtain non-study drug through usual means.	Clarification
4.4 End of Study Definition	Added Participants who will participate in the planned B7841007 long-term extension study are not required to	Clarification as these participants will be observed in the B7841007 study.

Section # and Name	Description of Change	Brief Rationale
	complete the ATP Day 390 Follow-up Phone Call.	
5.1 Inclusion Criteria	Added to Inclusion Criterion 4 Participants who have documented inhibitors while on factor-replacement therapy but who do not meet the quantitative inhibitor criteria described in the prior bullet at the time of Screening (eg, participant with a previously documented high-titer inhibitor (≥5 BU/mL) and whose condition precludes re-challenge with FVIII or FIX replacement), may be considered for eligibility on a case-by-case basis with prior approval from the Pfizer Medical Monitor.	To provide flexibility to enroll special case of potential participants with previous documentation of high titer inhibitors whose condition precludes re-challenge with FVIII or FIX replacement.
5.1 Inclusion Criteria	Added to Inclusion Criterion 6 Participant, or legally authorized representative, or participant's caregiver	Clarification
5.2 Exclusion Criteria	Added to Exclusion Criterion 9 Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.	Addition to exclude participants who may be allergic to material used in the formulation in alignment with the IB and as per request of Japan PMDA.
5.2 Exclusion Criteria	Added to Exclusion Criterion 14 Previous exposure to PF-06741086 during participation in studies B7841002 and B7841003	Additional clarification regarding exclusion of participants who were on prior studies of PF-06741086.
Throughout	Changed preventive to "preventative"	Clarification
6.3. Measures to Minimize Bias: Randomization and Blinding	For the Participants in the Non-Inhibitor Cohort added: No detectable or documented history of inhibitors during the 12-month period prior to Screening, during the Observational Phase, and through the Day -7 Visit in the Active Treatment Phase. Participants in the Inhibitor Cohort added at the time of enrollment into the Observational Phase and at the	Multiple clarifications regarding participants in the Inhibitor Cohort. Additional statement added regarding the expectation that participants remain in the initially assigned cohort for the duration of the study.

Section # and Name	Description of Change	Brief Rationale
	Day -7 Visit in the Active Treatment Phase. • Participants who have documented inhibitors while on factor-replacement therapy but who do not meet the quantitative inhibitor criteria described in the prior bullet at the time of Screening may be considered for eligibility on a case-by-case basis with previously documented approval from the Pfizer Medical Monitor. All participants meeting the criteria for transitioning to the Active Treatment Phase that are noted above will receive SC prophylaxis treatment QW with PF-06741086 after completion of the Observational Phase. Any participant who no longer meets the criteria for the cohort to which they are assigned at Baseline (Visit 2) during the Observational Phase will be discontinued from the study.	
6.4 Study Intervention Compliance	Added Study drug will be administered once weekly. And Participants who miss the 150 mg dose during any week during the Active Treatment Phase will need to initially administer a 300 mg loading dose when dosing resumes, and then resume their prescribed dosing regimen (150 mg once weekly). Participants who previously met the protocol specified dose escalation criteria and are administered 300 mg once weekly are already receiving the equivalent of the loading dose via their once weekly dose. When l loading dose is required it is the only dose given on the dosing day. In such cases, the participant's usual once weekly dose will resume the week following loading dose	Additional details added regarding protocol-required study drug compliance.
Table 1 Permitted Homeostatic medication	Footnote c ~~c. Antifibrinolytic~~. Systemic antifibrinolytic agents or	Clarification of this class of excluded medicine.

Section # and Name	Description of Change	Brief Rationale
	medications known to influence platelet function (eg, aspirin or certain non-steroidal anti-inflammatory drugs) washout of ≥120 hours prior to administration of study drug on Day 0 through completion of ATP Day 360 (Visit 20) in the Active Treatment Phase.	
Table 1 Permitted Homeostatic medication	Footnote d Reasons for preventative treatment will be categorized as either*: a) Medical/Dental procedure; or b) Other.*	Clarification of this class of excluded medicine.
6.5.2.1. Observation and Active Treatment Phases	Systemic antifibrinolytic agents or medications known to influence platelet function (eg, aspirin or certain non-steroidal anti-inflammatory drugs) require a washout of ≥120 hours prior to administration of study drug on Day 0 through completion of ATP Day 360 (Visit 20) in the Active Treatment Phase. Use of these medications is permitted thereafter and other times during the study period.	Clarification of the required washout for systemic antifibrinolytic medication.
6.5.2.2 Active Treatment Phase And 6.5.3 Treatment of Breakthrough Bleeding	Added: Treatment with aPCC (eg, FEIBA and in regions where available, BYCLOT), in accordance with approved product labeling.	To clarify use of an aPCC, commonly used in Japan, BYCLOT.
Table 2 Approximate Blood Volume	Updated sample volume in Table 2	Updated sample volume to reflect Central laboratory specifications for sample analyses
8.1.2. Bleeding	~~CRFs~~Adverse Event CRFs, as applicable.	Clarification for data management.
8.1.4. Location of Bleeds	Note: ~~in the event~~ Until the eDiary is~~not~~ available, a paper diary may be used during the Observational Phase for the initial visits.	Clarification that paper diary is a backup in the event that eDiary is not available.
8.1.7.2. Site Responsibilities for ePRO System	ePRO System will be covered in detail in ~~documentation~~ training material and an instruction manual provided and ePRO System and training on the use of this system are specifically	Additional details regarding ePRO system added

Section # and Name	Description of Change	Brief Rationale
	and guidelines~~and~~ Good Clinical Practice (GCP), and applicable regulations/guidelines of any participating country.	
8.1.7.4. Patient Reported Outcomes (PROs) Assessments	pre-loaded with the 4 5 instruments and Observational Phase (OP) Baseline, ATP Visits 6, 7, 10, 12, 14, 16, and 20	Additional details regarding ePRO system added
Throughout	Oral temperature changed to "temperature"	Clarification added for site flexibility
8.3.1.1. Reporting SAEs to Pfizer Safety	All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately and under no circumstance should this exceed 24 hours from the time the site staff becomes aware of the event,	Clarification added to ensure compliance with timely and safety reporting.
8.3.3. Follow-up of AEs and SAEs	The Investigator should contact the Pfizer Medical Monitor to discuss the most appropriate way to manage the occurrence of a thrombotic event or situations (eg, sepsis and trauma) in which there may be increased activation of coagulation.	Additional guidance for management of these specific AEs.
8.4. Treatment of Overdose	For this study, any dose of PF-06741086 greater than ~~450~~ 600 mg within a 6 day	Updated per clinical pharmacology.
8.5. Pharmacokinetics	All efforts will be made to obtain the PK samples at designated visits and times as per the SoA.~~at the nominal time relative to dosing.~~	Clarification
8.6.1. Tissue Factor Pathway Inhibitor	Added Blood samples of approximately 2.7 mL (combined for both total and free TFPI), at each timepoint, to provide approximately 1.4 mL plasma, will be collected into appropriately labeled tubes	Clarification for updated sample volume in Table 2
8.6.3. Prothrombin Fragment 1 and 2 and D-dimer	Added Blood samples of approximately 2.7 mL (combined for Anti Thrombin III, Prothrombin	Clarification for updated sample volume in Table 2

Section # and Name	Description of Change	Brief Rationale
	Fragment 1+2, and D-dimer) will be collected into appropriately labeled tubes	
Section 8.8.1	8.8.1. Analysis of Anti-~~PF-06741086~~Drug Antibodies and Neutralizing ~~Anti PF-06741086~~ Antibodies to PF-06741086 Blood samples of approximately 9.0 mL, to provide approximately 3.0 mL plasma, will be collected for determination of anti-~~PF-06741086~~drug antibodies (ADA) and neutralizing ~~anti PF-06741086~~ antibodies (NAb) to PF-06741086 as specified in the SoA (see Immunogenicity Tests in ATP) prior to administration of study intervention.	Clarification of terminology to minimize confusion
9.1.1. Estimands	All data during the preventative medical/dental treatment (plus 72 hours) is also excluded, see Section 6.3.	Updated as per the CHMP scientific advice.
9.4.3. Other Analyses	Added In the event a full dose cannot be administered, a partial dose will be reported and partial doses will be imputed using 50% of the full dose for each injection.	Added as per data management.
9.5 Interim Analysis	An interim analysis for futility will be performed when ~~for the first cohort that achieves completion of the Active Treatment Phase for~~ 50% of the planned number of participants either completes or drops off from the ATP for each of ~~among~~ the following 3 participant populations of interest: Inhibitor Cohort; Non-Inhibitor Cohort with prior On-Demand therapy for the US, Canada, and all regions outside of the EU; Non-Inhibitor Cohort with prior Prophylaxis. ~~At the time each individual primary endpoint is analyzed, interim analyses on the remaining portion(s) of the study may be performed to evaluated futility of the remaining portion of the study.~~	The timing for interim analyses for futility was changed to 50% of information time for each cohort to reduce the uncertainty in planning while preserving the purpose of the analyses. Clarification of populations for Interim Analysis

Section # and Name	Description of Change	Brief Rationale
	Upon completion of follow-up for each of the participant populations (Inhibitor Cohort; Non-Inhibitor Cohort with prior On-Demand therapy for the US, Canada, and all other regions outside of the EU; Non-Inhibitor Cohort with prior Prophylaxis) ~~individual specific primary endpoints (ABR in the Inhibitor Cohort; ABR in the Non Inhibitor Cohort vs. On-Demand for the US, Canada, and all regions outside of the EU; ABR in the Non Inhibitor Cohort vs Prophylaxis)~~ analyses of the primary endpoint of interest along with secondary endpoints in the corresponding participant populations ~~(Inhibitor Cohort; Non Inhibitor Cohort with prior On-Demand therapy for the US, Canada, and all regions outside of the EU; Non Inhibitor Cohort with prior Prophylaxis)~~ will be performed to assess respective efficacy and safety for a potential initial Biologic License Application filing and these analyses will be considered the final analysis for that participant population ~~of interest.~~	
Appendix 1	To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card and instructed to always carry the contact card and present to medical personal if medical treatment is required.	Added per request of Japan PMDA
Appendix 7	**For the investigator sites in Japan only:** **Section 6.5.3. Treatment of Breakthrough Bleeding** *Underline text added in place of strike-through* For inhibitor participants who experience breakthrough bleeding during the Active Treatment Phase which, in the clinical judgment of the investigator or delegated treating physician requires additional	Added per request of Japan PMDA

Section # and Name	Description of Change	Brief Rationale
	hemostatic therapy beyond PF-06741086 prophylaxis, ~~rFVIIa may be administered at the lowest effective dose but not to exceed 90 µg/kg per dose and not to exceed a dosing frequency of approximately every 2 hours.~~ For the participants in Japan, rFVIIa, the first dose should be 90 µg/kg and the second or later dose should be 60~90 µg/kg and not to exceed a dosing frequency of approximately every 2 hours. The investigator should confirm participant's understanding at the beginning of the trial regarding the determination of the necessity of administration of hemostatic treatment for breakthrough bleeding and the appropriate dosage. Whenever possible, before the participant or parent/caregiver administers the drug for breakthrough bleeding episodes, the participant should contact the investigator to confirm the necessity of the hemostatic treatment. **Section 10.1.3. Informed Consent Process** Following Text added: For Japanese participants under 20 years of age, it is necessary that the participant's parent or a caregiver, etc. sign the informed consent form, regardless of whether the participant has signed the assent document.	
Appendix 12	Updated entirely	To reflect the final SAP

Amendment 1, 25 April 2019

Overall Rationale for the Amendment:

The protocol was amended based on feedback from the United States (US) Food and Drug Administration (FDA).

Section # and Name	Description of Change	Brief Rationale
Throughout	For prophylaxis treatment, language was added to clarify that it applies	Addition of Canada is based on Health Canada's alignment with the FDA's position for not enrolling

Section # and Name	Description of Change	Brief Rationale
	only to participants outside the US and Canada.	participants previously on stable prophylaxis treatment regimen.
Throughout	Removal of "registration" and "health authority" when referring to US or EU regulatory agencies	This was removed per request from the FDA.
1.2 Schema and 4.1 Overall Design	Study schematic was updated.	This was updated per request from the FDA.
Schedule of Activities, Observational Phase	Paper diary may be used during the Observational Phase for the initial visits.	This allows for completion of diary entries until the electronic diary can be distributed for use at investigator sites.
Schedule of Activities, Active Treatment Phase	Immunogenicity sampling on Day 7 was moved to Day 28.	This was updated per request from the FDA.
Schedule of Activities, Active Treatment Phase	ATP Day 30 Phone Call was modified to ATP Day 28 Visit and additional assessments added	This phone call was revised to a site visit to accommodate immunogenicity sampling.
Schedule of Activities, Active Treatment Phase	Assessment of prior treatment was removed.	This was clarified for the Active Treatment Phase as participants are already assessed for prior treatments during the Observational Phase.
Schedule of Activities, Active Treatment Phase	Factor V Leiden mutation, prothrombin 20210 mutation, protein C activity, protein S level assessment is analyzed the day they are collected.	Samples will be analyzed for later comparison instead of being stored to minimize risk to sample instability over time.
Throughout	Country-specific language for sites in the US will also include Canada and clarifies only on-demand participants will be enrolled at these sites.	Addition of Canada is based on Health Canada's alignment with the FDA's position for not enrolling participants previously on stable prophylaxis treatment regimen.
5.2 Exclusion Criteria	Exclusion criterion for estimated glomerular filtration rate was revised from 60 to 30 mL/min/1.73 m^2.	This was updated per request from the FDA to include evaluation of participants with moderate renal impairment.
Schedule of Activities and 6 Study Intervention	Study intervention may be administered by study staff at the study center when needed.	This clarified procedures for administering study intervention when necessary to ensure participant safety and compliance with study intervention administration.
6.5.2.2 Active Treatment Phase	Emicizumab was added as a prohibited therapy during the Active Treatment Phase.	Prohibited therapy was updated to include a recently approved product.

Section # and Name	Description of Change	Brief Rationale
6.6 Dose Modification	Exclusion of bleeding data for decisions on dose modification was revised to from 30 days to 72 hours.	This was updated per request from the FDA to not exclude data from the first 30 days of dosing. Initial 72 hours of bleeding data will be excluded to allow efficacy evaluation of PF-06741086 once steady-state is achieved.
7.1 Discontinuation of Study Intervention	Individual level stopping and dose adjustment and study level stopping rules were added.	This was updated per request from the FDA.
7.2 Participant Discontinuation/Withdrawal from the Study	Removed thromboembolic events as criterion for discontinuation from the study.	This is redundant with criteria added in Section 7.1.
7.2 Participant Discontinuation/Withdrawal from the Study	"Substantial" was added to clarify withdrawal due to changes to prophylaxis regimen.	This clarified that minor changes to prophylaxis regimen would be acceptable.
8 Approximate Blood Volume Table	Blood volumes were modified based on additional PF-06741086 and immunogenicity sampling.	This was updated to account for additional samples and minor correction to volume for safety labs.
8.1.7 Patient-Reported Outcomes	Paper versions may be used during the Observational Phase for the initial visits.	This allows for completion of outcomes measures by paper until the electronic diary can be distributed for use at investigator sites.
9.4.1 Efficacy Analyses	Analyses of secondary endpoints was revised.	This was updated per request from the FDA.
9.5 Interim Analyses	An additional interim analysis was added for futility assessment.	This was updated per request from the FDA.
10.3.1 Definition of AE	Removed statement regarding events meeting adverse event definition.	Statement removed applies to non-efficacy studies in marketed products and is not applicable for this study.
10.3.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Assessment of intensity was updated to the Common Terminology Criteria for Adverse Events.	This was updated to allow assessment of intensity to accommodate individual and study stopping rules.
Throughout	Minor editorial changes	Minor, therefore have not been summarized

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