A PHASE 1, SINGLE-ARM, OPEN-LABEL, NON-RANDOMIZED, NON-CONTROLLED MULTICENTER STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, SAFETY, AND TOLERABILITY OF A SINGLE SUBCUTANEOUS DOSE OF PF-06741086 IN CHINESE ADULT PARTICIPANTS WITH SEVERE HEMOPHILIA

Investigational Product Number:	PF-06741086
Investigational Product Name:	Marstacimab
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2018-003660-31
Protocol Number:	B7841010
Phase:	1

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
Protocol Amendment 1	22-Oct-2020	Please see Overall Rationale for Amendment 1 below
Original protocol	24-Oct-2019	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs .

Overall Rationale for Amendment 1:

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.

CCI [redacted]

Additional edits resulted from internal review to correct errors, to make updates and include alternative study procedures information during the COVID-19 pandemic.

Section # and Name	**Description of Change**	**Brief Rationale**
Header	Changed to xx October 2020	Changed to reflect the final Amendment 1
Throughout	Changed "~~one way~~" to "single-arm"	Correction of error
Objectives and Endpoints Table	Primary Endpoint: Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAE; Day 1 up to Day ~~28~~ 42	Revised to be consistent with additional follow-up added in SoA.
Throughout	Added clarification that tissue factor pathway inhibitor (TFPI) samples were for both total and free TFPI.	Clarification
1.1Synopsis Intervention Groups and Duration	Following this 7 day period, all participants will return for outpatient follow-up visits once a week to Day ~~28~~ 42 per Schedule of Activities. The total duration of the study for a single subject, from initial screening to final follow-up, will be approximately ~~2~~ 2.5 months.	Revised to be consistent with additional follow-up added in SoA.
Schedule of Activities	Added: Alternative study visit information pertaining to the COVID-19 pandemic is	Reference was added to new appendix describing alternative study procedures during COVID-

	described in Appendix 9 (Section 10.9).	19 pandemic.
Schedule of Activities	Added visit Day 42 in column of follow-up	CCI [redacted]
Schedule of Activities	Deleted Hematology test in Day 1 (2hr,8hr,12hr post injection), Day 3 and 4. Deleted Factor VIII or Factor IX activity in Day 7. Deleted PT/INR, APTT, Fibrinogen, ATIII in Day1 (1hr, 4hr, 12hr post injection), Day 3 and 4; added PT/INR, APTT, Fibrinogen, ATIII tests in Screening visit. Deleted Cardiac Troponin I in Day1 (4hr and 12hr post injection) and Day3.	Deleted unnecessary safety tests in order to reduce the total blood draw volume.
Schedule of Activities	Added the safety monitoring from Screening to Day 42 in rows of Collect information on new bleeding episodes, Serious and non-serious adverse event monitoring, Concomitant medication.	Revised to ensure the safety monitoring of participants.
Schedule of Activities Footnote	e. ~~To note Day7 is exempt.~~	Revised to be consistent with FVIII or FIX activity test deleted in Day 7.
Schedule of Activities Footnote	g. Single ECGs will be required at all additional timepoints unless ECG or troponin I is abnormal.	Added for clarification.
Schedule of Activities Footnote	Added: j.The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator. CCI [redacted]	Clarification
Schedule of Activities Footnote	Added: k. Assessments for study early discontinuation or termination refer to Day 7 visit. To note that cTnI should be assessed if discontinuation/termination occurs prior to Day 4. ADA and NAb sample will be also collected in case of study early discontinuation or termination.	Clarification
Throughout	Changed "Limited physical examination" to "brief physical examination"	Revised for accuracy
Throughout	Changed "FIB" to "Fg"	Revised for accuracy
Section 2.2.3 Clinical Overview	~~There are no clear or emerging safety signals for PF-06741086 at the 3 dose levels studied in hemophilia A and B participants without inhibitors or in the data available for hemophilia A or B participants with inhibitors. Injection site reactions are considered adverse drug reactions for marstacimab.~~ The most	Updated safety data according to the final CSR of B7841002.

	common treatment-emergent and treatment-related AEs CCI [redacted] were injection site bruising CCI [redacted] hypertension CCI [redacted] injection site swelling CCI [redacted] and headache CCI [redacted] There have been no treatment related SAEs. No thrombotic events were reported in the study. No deaths occurred in the study. CCI [redacted] ~~he 300 mg SC QW and 150 mg SC QW regimens were generally safe and well tolerated. Severe, Grade 3 injection site reactions were reported for the 450 mg SC QW regimen (3 injections each with a 1.5 mL injection volume to deliver a 450 mg dose), suggesting that the limits of tolerability were observed for some (N=2) participants on this regimen. Among 26 participants treated with PF-06741086, no participants had positive ADA samples (titer ≥1.53) at baseline.~~	
Throughout	Changed "follow up" to "follow-up"	Correction of spelling mistakes
Section 2.3 Benefit/Risk Assessment	The nonclinical and clinical safety profile of PF-06741086 has been adequately characterized to support evaluation of the current clinical study in the Chinese hemophilia population. Participation in this study may benefit future patients with hemophilia. Potential Benefits The study participation can contribute for the justification of ethnic sensitivity assessment of PF-06741086 in Chinese hemophilia population. CCI [redacted] Additionally, weekly SC dosing with PF-06741086 may substantially reduce the burden of care associated with prophylactic treatment, eliminating the need for frequent IV infusions, potentially obviating the need	Expanded overall Benefit/Risk Assessment CCI [redacted]

	for indwelling central venous catheters, and reducing or eliminating 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.	
Section 4.1 Overall Design	Added: The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator. CCI [redacted]	Clarification additional follow-up added
4.2 Scientific Rationale for Study Design	This population also ~~represents those~~ matches the entry criteria for the global pivotal Phase 3 study.	Revised for clarity.
5.1 Inclusion Criteria	Age ~~and~~, Sex and Weight: 1. Participant must be male and 18 to <75 years of age with a minimum body weight of 30 kg ~~inclusive~~ at the time of signing the informed consent	Added body weight to be consistent with global Phase 3 study Inclusion Criteria.
5.1 Inclusion Criteria	3. No detectable or documented history of inhibitors (≥0.6 BU/mL or greater than the	Deleted to correct error.

	upper limit of normal [ULN] for the testing laboratory) against FVIII or FIX prior to enrollment. ~~OR~~	
5.1 Inclusion Criteria	Revised: 3. Participants with on-demand treatment regimen with ⩾6 acute bleeding episodes (spontaneous and/or traumatic) that required coagulation factor infusion during the ~~6~~ 4 months period prior to Screening 4. with FVIII or FIX recovery <60% of expected within ~~6~~ 4 months prior to screening. with bypass factor for at least ~~6~~ 4 months prior to screening	CCI [redacted]
5.2 Exclusion Criteria	Added: 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
5.2 Exclusion Criteria	Added: 10. A positive urine drug screen	Added to exclude participants with a positive urine drug test.
6.2.2 Allocation to Investigational Product	Added: This is an open-label, single-arm study.	Clarification
6.2.2 Allocation to Investigational Product	Changed "Investigational product" to "Study intervention"	To comply with the updated protocol template.
6.4.1 Prohibited Medication	Remove "PCC" from prohibited medication	Revised based on local clinical practice.
6.4.1 Prohibited Medication	Revised: through Day ~~28~~ 42 is prohibited.	Revised to be consistent with additional follow-up added.
6.4.2 Treatment(s) for Bleeding Episodes	Added in hemostatic therapy: or PCC at the lowest effective dose, in accordance with the Product Prescribing Information	Added the recommendation of use of PCC based on local clinical practice.
6.4.2 Treatment(s) for Bleeding Episodes	Revised: If a participant experiences a bleeding episode during the PK assessment period following administration of PF-06741086, the participant is to be stabilized utilizing the ~~participant's usual~~ Factor VIII or Factor IX treatment regimen at the lowest effective dose according to ~~product labeling~~ the approved Product Prescribing Information, or rFVIIa bypass agent therapy at approximately 90 µg/kg and not to exceed a dosing frequency of every 2 hours, or PCC at the lowest effective dose, in accordance with the Product Prescribing Information, and protocol specified observations and	Revision for clarification of treatment of bleeding episodes in different period.

	procedures should proceed to completion. If a participant experiences a bleeding episode after Day 28 following the initial administration of PF-06741086, the participant is to be stabilized utilizing the participant's usual hemostatic treatment regimen.	
7.1 Discontinuation of Study Intervention	Revised: Since this is a single-dose study, this section is not applicable. ~~In rare instances, it may be necessary for a participant to permanently discontinue investigational product. If investigational product is permanently discontinued, the participant will withdraw from the study. If a clinically significant finding is identified pre-dosing, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Any new clinically relevant finding should be reported as an AE. 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~~	Revised according to the appropriate protocol template.
7.2 Participant Discontinuation/Withdrawal From the Study	Revised: 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; • ~~or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.~~	To comply with the updated protocol template.
7.2 Participant Discontinuation/Withdrawal From the Study	Revised: See the SoA (visit Day 7) for assessments	Added missed assessment for discontinuation in SoA.
7.2 Participant Discontinuation/Withdrawal From the Study	Revised: If a participant withdraws from the study, he may request destruction of any remaining samples taken and not tested, ~~but data already generated from the samples will continue to be available, and may be used to protect the integrity of existing analyses.~~ 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 (see ~~below~~	Revised based on the new protocol template.

	Section 7.2.1) for disclosure of future information	
Section 8 Table 3 Blood Volume	Updated sample volume in Table 3	Updated sample volume to reflect central &local laboratory specifications for sample analyses
Section 8	**Added: 8.1. Efficacy Assessments** **Not applicable.**	Mandatory section in new protocol template
8.2.3 Electrocardiograms	Revised: At each time point at which triplicate ECG are required (ie, when single ECG is abnormal or when troponin I is abnormal), ~~3 individual ECG tracings should be obtained abnormal or when troponin I is abnormal)~~	Deleted the repeated content
8.2.3 Electrocardiograms	Changed "Appendix 7" to "Appendix 6"	
8.2.3 Electrocardiograms	Revised: the triplicate ECG measurements collected ~~at each nominal time point during Observational Phase Visit~~ at pre-dose Day1 will serve as each participant's baseline value.	Correction of error.
8.2.5 Injection Site Reaction	Deleted: ~~Participants will be provided written instructions and will be trained by study staff on the ment of injection site reactions.~~	Deleted inappropriate content.
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Revised: ~~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 case report form (CRF), not the AE section.~~ 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, and Pfizer concurs with that assessment. 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 definitively 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 AEs or SAEs after conclusion of the study participation. However, if the	To comply with the updated protocol template.

	investigator learns of any SAE, including a death, at any time after a participant has been discharged from 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.	
8.3.1.2 Recording Nonserious AEs and SAEs on the CRF	Revised: All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.2.1, 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. ~~During the active collection period, both nonserious AEs and SAEs are recorded on the CRF.~~	To comply with the updated protocol template.
Section 8.3	Added: 8.3.8. Adverse Events of Special Interest Not applicable.	To comply with the updated protocol template.
Throughout section 8.3.9 Medical Device Deficiencies	Changed "device incidents or malfunctions" to "device deficiencies" Changed "device incident" to "device deficiency" Changed "Appendix 8" to "Appendix 7"	To comply with the updated protocol template.
8.3.9.2 Follow-up of Medical Device 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 8.2.3). This applies to all participants, including those who discontinue study intervention.~~	To comply with the updated protocol template.
8.3.9.3 Prompt Reporting of Device Deficiencies to Sponsor	Device deficiencies ~~incidents~~ 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. 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 Section 8.3.1.1 and 8.3.1.2	To comply with the updated protocol template.
8.4 Treatment of Overdose	Revised: 2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities ~~until PF-06741086 can no longer be detected systemically (at least 21 days)~~ for at least 5 half-lives or 28	Revised according to treatment over dose in global Phase 3 protocol amendment 4 and to comply with the updated

	calendar days after the overdose of study intervention (whichever is longer) 3. Obtain 2 blood samples (7 days apart) for pharmacokinetic (PK) analysis within 7 ~~28~~ days from the date of the last dose of study intervention	protocol template.
Section 8.5.2	Analysis of Anti-PF-06741086 Antibodies and Neutralizing Antibodies to ~~Anti~~ PF-06741086 ~~Antibodies~~ Blood samples of approximately ~~4.5~~ 9.0 mL, to provide approximately ~~2~~ 3.0 mL plasma, will be collected for determination of anti-PF-06741086 antibodies (ADA) and neutralizing antibodies (NAb) to ~~anti~~ PF-06741086 ~~antibodies.~~ ~~Each plasma sample will be divided into 2 aliquots (1 for ADA, 1 for NAb).~~	Revised for accuracy and updated sample volume to comply with central lab requirement.
8.6 Pharmacodynamic	Revised: Biomarker concentration data (TFPI [total and free], Thrombin generation, PF1+2, D-dimer, and dPT)	Revised for accuracy
8.6.1 Tissue Factor Pathway Inhibitor	Revised: 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.	Revised for accuracy
Section 8.6.2	**Thrombin Generation Assay**	Revised for accuracy
Section 8.6.3	**Prothrombin Fragment 1 and 2 (PF1+2) and Dilute Prothrombin Time (dPT)** Blood samples of approximately 4.5 mL (combined for PF1+2 and dPT) will be collected into appropriately labeled tubes containing sodium citrate to provide ~~2 aliquots of 500 µL~~ approximately 1.0 mL plasma for PF1+2 analysis and approximately 1.0 mL plasma for dPT analysis, ~~each (1 for routine testing, 1 as back up) for PF1+2 and dPT analyses, and 2 aliquots of approximately 400 µL plasma each (1 for routine testing, 1 as back up) for coagulation tests analysis of D-dimer~~ as specified in the SoA	Revised for accuracy
Section 8.6.4	Moved down: **D-dimer** Blood samples of approximately 1.8 mL will be collected into appropriately labeled tubes containing sodium citrate to provide approximately 900 µL plasma for D-dimer analysis as specified in the SoA. Instructions for the collection and handling	Separated D-dimer as a new section for accuracy

	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.	
8.7.1 Specified Genetics	Revised: ~~Genetics (specified analyses) are not evaluated in this study.~~ A 5mL blood sample for DNA isolation will be collected. DNA samples will be analyzed for the purpose of assessing Factor V Leiden mutation and prothrombin 20210 mutation only at screening. No other genetic assessments are conducted.	Corrected genetics testing content.
9.3 Populations for Analysis	Added population description table	Updated according to new protocol template
9.5.1 Electrocardiogram Analyses	**Added section 9.5.1**	To comply with new protocol template
10.2 Appendix 2 Table 6	Added "Microscopy & Culture[a]" in urinalysis column Added "urine drug screening[d]" in Other column Added "Total bile acids" in Hy's law column Revised "a. Only if urinalysis is positive for blood, protein, leukocyte or nitrites" in foot note Added "d. At Screening and Day -1 only. Minimum requirement for drug screening includes:cocaine, tetrahydrocannabinol(THC), opiates/opioids,benzodiazepines and amphetamines." in foot note.	Revised for accuracy.
10.3 Appendix 3	Added in "**Events Meeting the AE Definition" :** • Is associated with accompanying symptoms; • Requires additional diagnostic testing or medical/surgical intervention; • 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.	To comply with new protocol template.
10.3.2. Definition of SA	Added in the table: **f. Other situations:** 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	To comply with new protocol template.

	serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.	
10.3.3 Recording/Reporting and Follow-up of AEs and/or SAE	**Changed "~~none~~" to "**All AEs/SAEs associated with exposure during pregnancy or breastfeeding.Occupational exposure is not recorded" in column of "**Recorded on the CRF"** **Added "**Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure." in column of "**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness"**	To comply with new protocol template.
10.5.	Added Section Appendix 5: Genetics	To comply with new protocol template.
10.6 Appendix 6: Liver Safety	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, gammaglutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase at the discretion of the investigator.	Revised for accuracy
10.8 Appendix 8	Updated the whole section **"Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting"**	To comply with new protocol template.
10.10 Appendix 10: Alternative Measures During Public Emergencies	Added new appendix	New appendix was added describing alternative study procedures during COVID-19 pandemic.

TABLE OF CONTENTS

LIST OF TABLES

CCI [redacted]

LIST OF FIGURES

No table of figures entries found.

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1 Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of a Single Dose of PF-06741086 in Chinese Adult Participants with Severe Hemophilia

Rationale:

Hemophilia is an X-linked recessive bleeding disorder caused by a deficiency of coagulant Factor VIII (FVIII) in hemophilia A or coagulant Factor IX (FIX) in hemophilia B. Patients with severe hemophilia often experience spontaneous bleeding episodes into joints, muscles and soft tissue, or even life threatening hemorrhage such as intracranial bleeding. The current standard medical care for severe hemophilia is prophylaxis replacement with FVIII or FIX clotting factor concentrate. In addition to minimizing hemophilic bleeds, these medications also play a key role in preventing the development of hemophilic arthropathy and improving patients' quality of life (QoL).[1] However, the frequent intravenous injections can be burdensome for patients and development of neutralizing antibodies, inhibitors directed against clotting factor in a subset of patients remains problematic of traditional factor replacement therapy.

According to 2017 annual survey report of World Federation of Hemophilia (WFH), there are 14,390 cases of hemophilia patients registered in China's National Hemophilia Information Management Center.[2] However, in China the estimated hemophilia population is about 65,000 to 130,000 based on a total population of 1.3 billion.[2-4] Most people with hemophilia (PWH) are under on-demand factor replacement therapy (on-demand therapy is only factor replacement to treat emergent bleeding events) because of low economic status, drug shortages and unbalanced insurance development among different areas.[5-7] Compared with developed countries, PWH in China had a higher annual bleeding rate, more hemophilia related disabilities and lower QoL due to the lack of the standard of care or prophylaxis treatment.[4] Although significant progress has been made in the past 10 years, further improvement of medical care for Chinese PWH is still needed and it's also important to explore new treatment approach to overcome the disadvantages of factor replacement therapy.

PF-06741086 is a human monoclonal immunoglobulin G isotype, subclass 1 (IgG1) that targets the Kunitz-2 domain of tissue factor pathway inhibitor (TFPI). It shows satisfactory safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) data both in Phase 1 first-in-human study (B7841001) and Phase 1b/2 first-in-patient study (B7841002) to support the development of PF-06741086 as a prophylactic treatment in severe hemophilia A and B with or without inhibitors. The existing studies did not involve Chinese participants, therefore, this study, B7841010, is designed to characterize the PK, PD, safety and tolerability of PF-06741086 following administration of a single subcutaneous (SC) dose in Chinese adult participants with severe hemophilia A or B, with or without inhibitor. CCI [redacted]

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
To determine the safety and tolerability of a single SC dose of PF-06741086 administered to Chinese adult participants with severe hemophilia A or B, with or without inhibitors.	• Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAE; Day 1 up to Day 42. • Frequency and magnitude of abnormal laboratory findings (including hematology, prothrombin time (PT)/ international normalized ratio (INR), activated partial thromboplastin time (APTT), chemistry, urinalysis, fibrinogen, anti-thrombin III (ATIII) activity and cardiac troponin I (cTnI)); Day 1 up to Day 28. • Changes from baseline in vital sign (blood pressure, pulse rate, temperature and respiration rate) measurements, 12-lead electrocardiogram (ECG) parameters and physical examination; Day 1 up to Day 28. • Frequency, severity and causal relationship of injection site reactions; Day 1 up to Day 7.
Secondary:	**Secondary:**
• To characterize the PK profile of a single SC dose of PF-06741086. • To characterize the PD profile of a single SC dose of PF-06741086.	• Plasma PF-06741086 concentrations as determined by a validated assay from Day 1 up to Day 28, and noncompartmental PK parameters including peak or maximum observed concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}), area under the concentration-time curve from time 0 to infinity (AUC_{inf}), terminal half-life, apparent volume of distribution (V_z/F), apparent clearance (CL/F). • TFPI (total and free); Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); Prothrombin fragment 1+2 (PF1+2);

• To characterize the immunogenicity of a single SC dose of PF-06741086.	D-dimer; Dilute prothrombin time (dPT); Day 1 up to Day 28. • Frequency of anti-drug antibody (ADA) and neutralizing antibody (NAb) production against PF-06741086; Day 1 up to Day 28. Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay.

Overall Design

This is a Phase 1, single-arm, open-label, non-randomized, non-controlled, multicenter study in 6 Chinese adult participants between ages 18 to <75 years with severe hemophilia A or B (defined as Factor VIII (FVIII) or Factor IX (FIX) activity <1%, respectively), with or without inhibitor. This study aims to evaluate the PK, PD, safety and tolerability of a single subcutaneous (SC) dose of PF-06741086.

Number of Participants

Approximately 6 participants are planned for enrollment at 2 study sites.

Intervention Groups and Duration

Participants who meet the selection criteria will accept a single SC injection of 300 mg PF-06741086 and go through a 7 day evaluation after dosing (including intensive PK) while confined in the study center. Following this 7 day period, all participants will return for outpatient follow-up visits once a week to Day 42 per Schedule of Activities. The total duration of the study for a single subject, from initial screening to final follow-up, will be approximately 2.5 months.

Data Monitoring Committee: No

Statistical Methods

Statistical objective is exploratory. Descriptive analyses will be performed.

1.2. Schema

Not applicable.

1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Alternative study visit information pertaining to the COVID-19 pandemic is described in Appendix 10 (Section 10.10).

Protocol Activity	**Screening**		**Clinical confinement**											**Follow-up Visits**			
Visit Identifier	**Screening**	**Day -1**	**Day 1**							**Day 2**	**Day 3**	**Day 4**	**Day 7[k]**	**Day 14**	**Day 21**	**Day 28[i]**	**Day 42[j]**
Visit Window	**Day -35 to Day -2**												**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**
Planned Time Pre/Post Dose			**-2 hr to -5 min**	**0 hr**	**1 hr ±10 min**	**2 hr ±10 min**	**4 hr ±20 min**	**8 hr ±0.5 hr**	**12 hr ±1 hr**	**24 hr ±2 hr**	**48 hr ±4 hr**	**72 hr ±7 hr**					
Informed consent	X																
Medical history	X	X															
Medication history	X	X															
Physical examination[a]	X	X											X			X	
Demography, Height	X																
Weight	X	X											X			X	
Urine drug screening	X	X															
Inclusion/exclusion criteria review	X	X															
Supine Vital Signs[b]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X		X							X			X				
Hematology[c]	X		X							X			X				
Serum chemistry	X		X							X			X				
Lipid profile[d]	X																
Factor VIII or Factor IX Activity[e]	X		X														
Factor VIII or Factor IX inhibitor levels	X																

Protocol Activity	**Screening**		**Clinical confinement**											**Follow-up Visits**			
Visit Identifier	**Screening**	**Day -1**	**Day 1**							**Day 2**	**Day 3**	**Day 4**	**Day 7[k]**	**Day 14**	**Day 21**	**Day 28[i]**	**Day 42[j]**
Visit Window	**Day -35 to Day -2**												**±1 day**	**±2 days**	**±2 days**	**±3 days**	**±7 days**
Planned Time Pre/Post Dose			**-2 hr to -5 min**	**0 hr**	**1 hr ±10 min**	**2 hr ±10 min**	**4 hr ±20 min**	**8 hr ±0.5 hr**	**12 hr ±1 hr**	**24 hr ±2 hr**	**48 hr ±4 hr**	**72 hr ±7 hr**					
Protein C activity/Protein S level	X																
Prothrombin 20210 mutation	X																
Factor V Leiden mutation Testing	X																
Serology: HbsAg, HBc Ab, HCV Ab, and HIV	X																
CD4 cell count[f]	X																
ECG[g]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Investigational Product administration				**X**													
CRU confinement		X	→	→	→	→	→	→	→	→	→	→	X				
PK blood sampling			X		X		X		X	X	X	X	X	X	X	X	
PD blood sampling[h]			X		X		X		X	X	X	X	X	X	X	X	
PT/INR	X		X							X			X	X	X	X	
APTT	X		X							X			X	X	X	X	
Fibrinogen	X		X							X			X	X	X	X	
Anti-thrombin III	X		X							X			X	X	X	X	
Cardiac Troponin I			X							X		X					
Immunogenicity (ADA, NAb)			X											X	X	X	
Monitoring injection site reactions				X	→	→	→	→	→	→	→	→	X				
Collect information on new bleeding episodes	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Protocol Activity	Screening		Clinical confinement											Follow-up Visits			
Visit Identifier	Screening	Day -1	Day 1							Day 2	Day 3	Day 4	Day 7[k]	Day 14	Day 21	Day 28[i]	Day 42[j]
Visit Window	Day -35 to Day -2												±1 day	±2 days	±2 days	±3 days	±7 days
Planned Time Pre/Post Dose			-2 hr to -5 min	0 hr	1 hr ±10 min	2 hr ±10 min	4 hr ±20 min	8 hr ±0.5 hr	12 hr ±1 hr	24 hr ±2 hr	48 hr ±4 hr	72 hr ±7 hr					
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant medication	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: → = ongoing/continuous event; ADA = anti-drug antibodies; APTT = activated partial thromboplastin time; CRU = clinical research unit; ECG = electrocardiogram; HBc Ab = hepatitis B core antibody; HBs Ag = hepatitis B surface antigen; HCV Ab = hepatitis C antibody; HIV = human immunodeficiency virus; hr = hours; min = minutes; N/A = not applicable; NAb = neutralizing antibodies; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio

a. The full physical examination (PE) planned for Screening may be performed on Day -1 before dosing at the discretion of the Investigator. If a full PE is done at Screening visit, then a brief PE is to be conducted on Day-1. After Day -1, brief examinations based on signs and symptoms will be performed if clinically indicated at the discretion of the Investigator to assess changes from baseline/previous visits of any ongoing symptoms.

b. Vital signs to be assessed include pulse rate, respiration rate, temperature, and supine blood pressure.

c. Differential hematology panel required at Screening, Day 1, and Day 7. Differential is optional at additional timepoints, as clinically indicated.

d. Participants must be fasting for 12 hours prior to blood draw.

e. A single sample to measure FVIII or FIX activity is to be collected after minimum washout period completed for prescribed factor-replacement product: FVIII replacement therapy for at least 72 hours; Extended half-life FVIII replacement therapy for at least 4× half-life; FIX replacement therapy for at least 96 hours; Extended half-life FIX replacement therapy for at least 4× half-life; bypass agent therapy from rFVIIa, prothrombin complex concentrate (PCC) or activated prothrombin complex concentrate (aPCC) for at least 72 hours.

f. CD4 cell count test if HIV positive.

g. Triplicate ECGs will be obtained at baseline pre-dose on Day 1. Single ECGs will be required at all additional timepoints unless ECG or troponin I is abnormal, in which case a triplicate ECG is required.

h. PD blood sample including assessments for: Tissue factor pathway inhibitor (TFPI) (total and free), Thrombin Generation Assay (TGA), Prothrombin fragment 1+2 (PF1+2), D-dimer, Dilute prothrombin time (dPT).

i. Participants with positive ADA results may be requested to return for additional follow-up visits after final planned follow-up visit.

j. The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator. CCI [redacted]

k. Assessments for study early discontinuation or termination refer to Day7 visit. To note that cTnI should be assessed if discontinuation/termination occurs prior to Day 4. ADA and NAb sample will be also collected in case of study early discontinuation or termination.

2. INTRODUCTION

PF-06741086 is a human monoclonal immunoglobulin of the 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 B, with or without inhibitors.

2.1. Study Rationale

The purpose of the study is to characterize the PK, PD, safety and tolerability profiles with a single subcutaneous (SC) dose of PF-06741086 in Chinese adult participants with severe hemophilia A or B, with or without inhibitor. CCI [redacted]

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.[8] Factor 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.[9] For patients who respond to clotting factor replacement, the intravenous (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 once weekly (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).[10] TFPI has 2 isoforms, TFPI α and TFPI β. The 2 isoforms share 2 of the same Kunitz type domains (K1 and K2), but TFPI β lacks the K3 domain. Isoforms are distributed in plasma and on vascular endothelial cell surfaces through glycosylphosphatidylinositol anchors. TFPI α 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.[11] 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.[12] These results suggest that TFPI may serve as an acceptable target for a pharmaceutical treatment to reduce inhibition of the extrinsic coagulation pathway and there by increase clotting activity in patients with

bleeding disorders, such as hemophilia.

2.2.1. Nonclinical Pharmacology and Pharmacokinetics

Analysis at the molecular level demonstrated that PF-06741086 targets an epitope in the K2 domain. Surface Plasmon Resonance (SPR) was used to characterize PF-06741086 binding affinity and kinetics of binding to human, cynomolgus monkey, rabbit, mouse, and rat TFPI [redacted] The neutralization of TFPI by PF-06741086 was measured using a number of in vitro functional assays. The analysis included FXa chromogenic activity assays which measure reversal of TFPI inhibition of Factor Xa or FXa/FVIIa/TF complex in purified systems. PF-06741086 promoted hemostasis in hemophilic plasma from hemophilia A, B, and hemophilia inhibitor plasma and in non-hemophilic plasma as measured in thrombin generation assays (TGA), and dilute prothrombin time (dPT) assays. PF-06741086 inhibitory activity was also demonstrated using thromboelastography (TEG) performed on whole non-hemophilic blood. PF-06741086 also improved the thrombin generation response of severe hemophilia plasma dosed with rFVIIa (eptacog alfa [activated]). The efficacy of PF-06741086 was demonstrated in injury models of hemostasis using Factor VIII deficient mice (model of hemophilia A) and Factor IX deficient mice (model of hemophilia B). PF-06741086 restored hemostasis in hemophilia mouse injury models when administered before and after the onset of a bleeding injury. The pharmacodynamic profile of PF-06741086 is consistent with its TFPI inhibitory activity.

The cumulative pharmacodynamic and potential additive effects of the combined, repeat-dose administration of PF-06741086 and NovoSeven® RT (rFVIIa) was evaluated in rats in a 10-day IV investigative study. [redacted]

CCI [redacted]

Separate safety pharmacology studies were not conducted with PF-06741086, but safety pharmacology endpoints evaluating the potential effects of PF-06741086 on the respiratory, cardiovascular (CV), and central nervous systems (CNS) were included in the 13-week toxicity study in monkeys.

The nonclinical pharmacokinetics (PK) strategy supported the nonclinical pharmacology and nonclinical safety evaluation of PF-06741086. The PK of PF-06741086 was characterized in Wistar Han rats, New Zealand White rabbits and cynomolgus monkeys following intravenous (IV) and/or subcutaneous (SC) dosing of PF 06741086. Validated assays were used to support the toxicokinetic (TK) and anti-drug antibody (ADA) evaluations in the repeat-dose toxicity and toxicokinetic studies in Wistar Han rat and cynomolgus monkeys conducted under Good Laboratory Practices (GLP). The pharmacokinetics-pharmacodynamic (PK/PD) relationships for PF-06741086 were characterized in cynomolgus monkeys.

Additional information regarding PF-06741086 may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure.

2.2.2. Nonclinical Toxicology

The toxicity of intravenously or subcutaneously administered PF-06741086 was evaluated in nonpivotal CCI [redacted] 8-day, repeat-dose studies in rats and monkeys and pivotal GLP studies in rats and monkeys CCI [redacted] The IV and SC routes of administration were selected for these studies since they are the intended routes of clinical exposure. Rats and monkeys were chosen as the nonclinical species because PF-06741086 binds to TFPI in these species. The use of rats and monkeys in nonclinical toxicology studies is further justified by evidence of pharmacological activity consistent with the activation of the coagulation cascade, such as decreases in fibrinogen (FIB) and increases in D-dimer, in both species in repeat-dose toxicity studies. Both species demonstrated drug exposure following IV or SC administrations, a possible target organ in both rats and monkeys was the coagulation cascade; therefore the rat was suitable for use as the only species for evaluating chronic toxicity. Other toxicity studies included a single-dose SC local toleration study in rats, a male fertility study in rats, tissue cross reactivity assay, Fc receptor (FcR) and complement 1q (C1q) binding assays, and a cytokine release assay. Genetic toxicity studies were not conducted because they are generally not appropriate for biotechnology-derived products. CCI [redacted]

PF-06741086 was administered to rats and monkeys by intravenous (IV) and subcutaneous (SC) injection, in studies up to 26 weeks in duration. CCI [redacted]

CCI [redacted]

A potential target organ identified in these studies was the coagulation cascade based on nonadverse changes in D-dimer, PT, APTT, and fibrinogen CCI [redacted] Prolongation of APTT and PT was not adverse because it was not associated with any test article-related clinical signs or test article-related microscopic findings consistent with hemorrhage. Changes in FIB, D-dimer, PT, APTT, and/or microscopic thrombi/emboli observed with PF-06741086 occurred without dose response, were of small magnitude or minimal severity, and, for the coagulation parameter changes in rats, had reversed at end of the recovery phase. Other effects on albumin (ALB), globulin (GLOB), ALB:GLOB and total protein values of rats and monkeys, the SC injection site of rats, and ADAs were observed in rats.

In tissue cross reactivity studies, staining with PF-06741086 was observed in membrane granules of human placental decidual cells, as well as in the cytoplasm, peripheral cytoplasm and/or cytoplasmic granules/globules of the endothelium from humans, monkeys and rats (including rat reticuloendothelium); placental trophoblasts from humans and monkeys and spongiotrophoblasts from rats; epithelium (including reticular epithelium) and tonsillar reticular cells from humans; and mesothelium, islet cells, and extra-cellular material of ovaries from monkeys.

CCI [redacted]

CCI [redacted] Additional information regarding PF-06741086 may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure (IB).

2.2.3. Clinical Overview

2.2.3.1. Overall Safety

To date, 2 clinical studies with PF-06741086 (B7841001 and B7841002) have been completed. B7841001 was a Phase 1, first-in-human (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. CCI [redacted]

The second completed Study B7841002 was a Phase 1b/2, open-label, multiple ascending dose study in participants with severe hemophilia A or B (≤1% factor activity). This study was designed to evaluate the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of PF-06741086. A total of 27 participants in 4 dosing cohorts (including 7 patients with inhibitors in Cohort 4) have been enrolled and received PF-06741086 via SC administration for prophylaxis against bleeding episodes over a 3-month treatment period. Twenty-four (24) patients have completed treatment including 6 patients with inhibitors.

CCI [redacted]

CCI [redacted]

Another study, B7841003, is ongoing. B7841003 is a long-term follow-up study to participants completing B7841002 and de novo hemophilia participants with inhibitors. In B7841003, up to 36 participants will be assigned to treatment with PF-06741086 for a continuous treatment period of at least 6 months. CCI [redacted]

2.2.3.2. Plasma Pharmacokinetics of PF-06741086

2.2.3.2.1. Following Administration of Single IV or SC Doses in B7841001

A summary of PK parameters following single dose SC administration of PF-06741086 at 30, 100, and 300 mg and single dose IV infusion over 1 hour at 150 and 440 mg is presented in Table 1.

Peak plasma concentration (C_{max}) was reached at 1 hour, ie, first sample collection at the end of infusion, following IV administration and 48 to 108 hours following SC administration. Under the same dosing route, exposures (particularly area under the curve (AUC)) appeared to increase greater than proportionally with dose, which suggests that PF06741086 may undergo target mediated drug disposition. As dose increases, mean terminal half-life ($t_{½}$) of PF-06741086 increased from 33.3 h (100 mg SC) to 79.5 h (440 mg IV) in non--Japanese participants. Mean values of C_{max} and area under the concentration time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}) were similar between the White participants and Japanese participants following PF-06741086 300 mg SC dosing indicating no apparent difference in PK based on observed data. Mean AUC_{inf} was moderately higher in Japanese participants due to one out of 2 Japanese participant reporting a $t_{½}$ of 122 hours and as a result of which, the extrapolated AUC_{inf} of the Japanese participant was outside the range observed in the non--Japanese participants.

CCI [redacted]

CCI [redacted]


CCI
CCI
CCI
CCI

2.2.3.3. Pharmacodynamics of PF-06741086

2.2.3.3.1. Following Administration of Single IV or SC Doses in B7841001

Pharmacologic effects reflective of coagulation pathway activation, which includes dPT, prothrombin fragment 1+2 (PF1+2), D-dimer, as well as the TGA parameters of lag time and peak thrombin generation, were monitored in Study B7841001. Total plasma TFPI level was also measured to reflect target binding.

Preliminary PD data following single dose SC administration of PF06741086 at 30, 100, and 300 mg and single dose IV infusion over 1 hour at 150 and 440 mg suggested that treatment related changes were observed for all PD endpoints and generally the response was exposure dependent. Pharmacologic effects on total TFPI as well as a number of PD biomarkers (eg, PF1+2, TGA lag time and thrombin generation, and D-dimer) persist >7 days following administration a single 300 mg SC dose of PF06741086. To support the planned weekly dosing following SC administration, area under the effect curve for change from baseline values (ie, 0H on Day 1) from Days 17 for each PD endpoint was calculated. While changes were observed at all dose levels for some PD endpoints (eg, TGA lag time and TGA thrombin generation), others were only observed at a higher dose level (eg, D-dimer, PF1+2 and dPT at 100 mg and above, and total TFPI at 150 mg and above). Maximum or near maximum effect occurred most frequently following a single dose of 300 mg SC based on these AUC values.

2.2.3.3.2. Following Administration of Multiple SC Doses in B7841002

Treatment related changes were observed for all PD endpoints in all dose cohorts as expected. CCI [redacted] There were no clinical findings suggesting that these PD changes were reflective of excessive pharmacology. PD responses were mostly consistent between inhibitor and non-inhibitor participants and between hemophilia A and B participants.

2.3. Benefit/Risk Assessment

The nonclinical and clinical safety profile of PF-06741086 has been adequately characterized to support evaluation of the current clinical study in the Chinese hemophilia population. Participation in this study may benefit future patients with hemophilia.

Potential Benefits

The study participation can contribute for the justification of ethnic sensitivity assessment of PF-06741086 in Chinese hemophilia population. CCI [redacted] Additionally, weekly SC dosing with PF-06741086 may substantially reduce the burden of care associated with prophylactic treatment, eliminating the need for frequent IV infusions, potentially obviating the need for indwelling central venous catheters, and reducing or eliminating 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.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of PF-06741086 may be found in the investigator's brochure (IB), which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
To determine the safety and tolerability of a single SC dose of PF-06741086 administered to Chinese adult participants with severe hemophilia A or B with or without inhibitors.	• Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAE; Day 1 up to Day 42. • Frequency and magnitude of abnormal laboratory findings (including hematology, PT/INR, APTT, chemistry, urinalysis, fibrinogen, ATIII activity and cardiac troponin I); Day 1 up to Day 28. • Changes from baseline in vital signs (blood pressure, pulse rate, temperature and respiration rate) measurements 12-lead electrocardiogram (ECG) parameters and physical examination; Day 1 up to Day 28. • Frequency, severity and causal relationship of injection site reactions; Day 1 up to Day 7.
Secondary:	**Secondary:**
• To characterize the PK profile of a SC single dose of PF-06741086.	• Plasma PF-06741086 concentrations as determined by a validated assay Day 1 up to Day 28, and noncompartmental PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf}, terminal half-life, V_z/F, CL/F.
• To characterize the PD profile of a SC single dose of PF-06741086.	• TFPI (total and free); Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); Prothrombin fragment 1+2 (PF 1+2); D-dimer; Dilute prothrombin time (dPT); Day 1 up to Day 28.
• To characterize the immunogenicity of a single SC dose of PF-06741086.	• Frequency of anti-drug antibody (ADA) and neutralizing antibody (NAb) production against PF-06741086; Day 1 up to Day 28. Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, single-arm, open-label, non-randomized, non-controlled, multicenter, study in 6 Chinese adult participants between ages 18 to <75 years with severe hemophilia A or B (defined as Factor VIII (FVIII) or Factor IX (FIX) activity <1%, respectively), with or without inhibitor. This study aims to evaluate the PK, PD, safety and tolerability of a single subcutaneous (SC) dose of PF-06741086.

Approximately 6 participants are planned for enrollment at 2 study sites. Participants who are withdrawn for any reasons may be replaced at the discretion of the investigator and after consultation with the sponsor. Participants will be screened within 35 days prior to administration of the investigational product to confirm that they meet the participant selection criteria for the study. Participants will be admitted into the Clinical Research Unit (CRU) 1 day prior to dosing (Day-1) and will accept a single SC injection of 300 mg PF-06741086 (150 mg *2) at Day 1. There is no dose modification plan during the study. Participants will be required to stay in the CRU through completion of the Day 7 evaluations. After that, it will be at investigator's discretion on whether the participants should stay in the CRU or not. All participants will return for weekly clinic visits on Day 14, Day 21, and Day 28 per the Schedule of Activities. The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator CCI [redacted]

Participants who experience a treatment-related adverse event (including lab abnormalitie

s) at any time point will continue to be followed through resolution or stabilization of the event as agreed upon by the investigator and sponsor.

The maximum total duration of the study for a single participant, from initial screening to final follow-up, will be approximately 2.5 months.

CCI [redacted]

4.2. Scientific Rationale for Study Design

Study B7841010 will be conducted in Chinese adult participants 18 to <75 years of age with severe hemophilia A or B, with or without inhibitor. This population also matches the entry criteria for the global pivotal Phase 3 study. The mechanism of action of PF-06741086 through the extrinsic cascade predicts it would be effective in both forms of hemophilia. Similarly, it is acceptable to enroll both those with inhibitors and those without, because the mechanism of action is not expected to be influenced by the presence of inhibitors to either FVIII or FIX. The clinical risk/benefit profile for this population is considered appropriate for the evaluation of PK, PD, safety and tolerability of PF-06741086.

The primary objective of Study B7841010 is to evaluate the safety and tolerability of a single SC dose of PF-06741086. Secondary objectives include evaluating the PK, PD properties and immunogenicity of PF-06741086. Selection of the PD endpoints and sampling schedule are based on results from non-clinical studies, the Phase 1 FIH study and Phase 1b/2 first-in patient (FIP) study results. They will reflect either target binding by PF-06741086 (ie, TFPI [total and free] levels) or downstream pharmacologic effects of TFPI inhibition (ie, dPT, TGA, PF1+2 and D-dimer). Thrombosis is a potential risk for inhibition of TFPI, and PF-06741086 is expected to significantly inhibit TFPI, particularly at the highest dose levels. To minimize this risk, hemophilia patients with a known history of thrombotic, ischemic or coronary artery disease, or known pro-thrombotic conditions (eg, Protein C deficiency) will be excluded from this study. Safety monitoring will include laboratory parameters that may be modulated due to coagulopathy (eg, [PT]/INR, APTT, fibrinogen, ATIII and platelet counts) and parameters to screen for possible thrombotic events (eg, cardiac troponin I). Laboratory endpoints to detect excessive modulation of the coagulation pathway will be monitored during the period of peak drug exposure, until at least 28 days have passed since the investigational drug administration.

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. An additional potential risk for treatment with PF-06741086 is ADA-induced hypersensitivity. Additional safety information for PF-06741086 is available in the IB.

Demonstration of PK, PD, safety and tolerability profile that is supportive for chronic treatment on an acceptable dosing schedule will permit progression to subsequent investigations in Chinese patients with severe hemophilia.

4.3. Justification for Dose

The purpose of this study is to characterize the PK, PD, safety and tolerability profiles following a single SC dose of 300 mg PF-06741086 in Chinese adult participants with severe hemophilia A or B, with or without inhibitor. CCI [redacted] The dose justification for this study is based on considerations outlined below.

CCI [redacted]

CCI [redacted] Phase 1 FIH study B7841001 and Phase 1b/2 FIP study B7841002.

CCI [redacted] 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. The PK parameters could not be characterized after the 30-mg dose administration, CCI [redacted]

CCI [redacted]

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-06291874 were evaluated CCI [redacted] Considerations included safety and tolerability, efficacy, PK and PD parameters, immunogenicity, and biopharmaceutics. CCI [redacted]

[redacted]

4.3.2. Dose justification of a single dose of 300 mg PF-06741086 SC in this study

A single 300 mg PF-06741086 SC proposed in this study CCI [redacted]

CCI [redacted]

- the dose administered to a cohort of 6 Western and a cohort of 4 Japanese subjects in B7841001 so that the intensive Chinese PK data, CCI [redacted] can be compared with that from the Western group in B7841001.
- the first dose administered to non-inhibitor subjects in Cohort 1 (300 mg QW) and Cohort 2 (a 300 mg loading dose, followed by 150 mg QW), and to inhibitor subjects in Cohort 4 (300 mg QW) of B7841002.

Based on the above justification, a single dose of 300 mg PF-06741086 SC is proposed for this China standalone study, CCI [redacted]

CCI [redacted]

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 last scheduled procedure shown in the schedule of activities.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the trial globally.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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 , Sex and Weight:

1. Participant must be male and 18 to <75 years of age with a minimum body weight of 30 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 B (FVIII or FIX activity <1%, respectively).

3. Participants **without inhibitor** 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.
   - Participants with on-demand treatment regimen with ≥6 acute bleeding episodes (spontaneous and/or traumatic) that required coagulation factor infusion during the 4 months period prior to Screening and willing to continue to receive on-demand treatment during the study. Surgical bleeding episodes do not apply to this criterion.

4. Participants **with inhibitor** 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 4 months prior to screening.
- Participants with on-demand treatment regimen with ≥6 bleeding episodes (spontaneous and/or traumatic) necessitating treatment with bypass factor for at least 4 months prior to screening and willing to continue to receive on-demand treatment during the study. Surgical bleeding episodes do not apply to this criterion.

Informed Consent:

5. Capable of giving signed informed consent 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 and/or history of coronary artery diseases, venous or arterial thrombosis (Common Terminology Criteria for Adverse Events [CTCAE][13] Grade >1), or ischemic disease (except treatment 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. Fibrinogen level <LLN
    c. Hemoglobin level <10 g/Dl

6. Abnormal coagulation activity as defined by the following laboratory results at Screening:
    a. Prothrombin time (PT) >1.25 × ULN.
7. 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.
8. Corrected QT interval (QTc) >450 msec for male participants or QTc >480 msec in participants with bundle branch block.
9. Individuals with hypersensitivity or an allergic reaction to hamster protein or other components of the study intervention.
10. A positive urine drug screen.

Prior/Concomitant Therapy:

11. Current routine prophylaxis with bypassing agent (eg, activated prothrombin complex concentrate (aPCC), Prothrombin Complex Concentrates [PCC], and/or rFVIIa) or non coagulation factor-replacement therapy (eg, emicizumab).
12. Regular, concomitant therapy with immunomodulatory drugs (eg, IV immunoglobulin [IVIG], and routine systemic corticosteroids, rituximab).
13. Ongoing or planned use of immune tolerance induction during the study phase, or prophylaxis with FVIII or FIX replacement during the study.

Prior/Concurrent Clinical Study Experience:

14. Participation in other studies involving investigational drug(s) within 30 days (or as determined by local requirements) or 5 half-lives prior to study entry and/or during study participation.

Diagnostic Assessments:

15. CD4 cell count ≤200/Ul if human immunodeficiency virus (HIV)-positive
16. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

Other Exclusions:

17. 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 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 serious adverse event (SAE).

Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should 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.

For the purposes of this protocol, the term investigational product may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

ARM Name	PF-06741086
Intervention Name	PF-06741086
Type	Biological product
Dosage Form	Injectable
CCI [redacted]	[redacted]
Dosage	300 mg once [a]
Route of Administration	Subcutaneous injection [b]
IMP and NIMP [c]	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.

CCI [redacted]

b. Following an overnight fast of least 10 hours, participants will receive PF-06741086 by SC injection at approximately 0800 hours (plus or minus 2 hours). All participants will be required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours

after dosing. The number of injections and injection sites will be recorded. The preferred body locations of the SC injections are the front of the middle thigh, including anterolateral, or outer area of the upper arm. If an arm is used for the SC injection, the opposite arm should be used for the PK/PD blood sample collections, if possible. CCI

[redacted]

c IMP= investigational medicinal product; NIMP= non-investigational medicinal product

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).

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

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). All study interventions will be accounted for using an investigational product accountability form/record.

4. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

6. Study interventions should be stored in their original containers and in accordance with the labels.

7. See the investigational product manual (IP manual) for storage conditions of the study intervention once reconstituted and/or diluted.

8. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.2.1. Preparation and Dispensing

See the investigational product manual (IP manual) for instructions on how to prepare the investigational product for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

6.2.2. Allocation to Investigational Product

This is an open-label, single-arm study. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant identification numbers sequentially to the participants as they are screened for the study. This identifying number will be retained throughout the study. A participant identifying number must never be reassigned or reused for any reason.

Study intervention will be dispensed at the study visits summarized in the Schedule of Activities (SoA).

Returned study intervention must not be redispensed to the participants.

6.3. Study Intervention Compliance

Participant compliance with investigational product will be assessed.

Compliance will be assessed by direct questioning. Deviation(s) from the prescribed dosage regimen should be recorded in the case report form (CRF).

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

6.4. Concomitant Therapy

Participants will abstain from all prohibited concomitant medications, except for the treatment of adverse events or acute bleeding episodes as described in Section 6.4.1 of this protocol.
All concomitant treatments taken during the study must be recorded with indication, and start and stop dates of administration. All participants will be questioned about concomitant treatments at each clinic visit. If a participant receives a prohibited concomitant medication during their participation in the study, the participant's continued participation in the study will be decided on a case-by-case basis, at the discretion of the investigator and sponsor.

For emergency or unplanned surgical interventions, investigators must contact the sponsor's medical monitor as soon as possible to review concomitant treatments and any impact on participant participation.

Treatments taken within 28 days prior to informed consent being signed will be documented as a prior treatment. Treatments taken from date of signed informed consent will be documented as concomitant treatments.

6.4.1. Prohibited Medications

Factor VIII (within 72 hours) or Factor IX replacement therapy (within 96 hours), extended half-life FVIII or FIX replacement therapy (within 4 x half-life) or bypass agent therapy (rFVIIa, PCC or aPCC: within 72 hours) before Screening is prohibited. Depending on the coagulation factor product in use, additional wash out time may be required prior to the screening assessments to achieve a factor activity level ≤1%. If a participant experiences an acute bleeding episode during this washout period requiring treatment with a Factor VIII or IX replacement therapy, or bypass agent therapy, the participant is to be stabilized utilizing this regimen and a new washout period should be initiated. The regimen used to treat the episode should be recorded as a prior medication.

Factor VIII (within 72 hours) or Factor IX replacement therapy (within 96 hours), extended half-life FVIII or FIX replacement therapy (within 4 x half-life) or bypass agent therapy (for rFVIIa, PCC or aPCC: at least 72 hours) before Day 1 treatment is also prohibited. If a participant experiences an acute bleeding episode during this washout period requiring treatment with a Factor VIII or IX replacement therapy, or bypass agent therapy the participant is to be stabilized utilizing this regimen and a new washout period should be initiated. The regimen used to treat the episode should be recorded as a concomitant medication. All acute bleeding episodes between Screening and Day 1 must be recorded. Treatment with **rFVIIa at a dose level greater than approximately 90 µg/kg and to exceed a dosing frequency of approximately every 2 hours is prohibited throughout the study**. If a participant receiving investigational product is subsequently administered a rFVIIa dose greater than approximately 90 µg/kg or more frequent than every 2 hours, the investigator must immediately contact the

sponsor's medical monitor to discuss the case to determine if the respective participant should continue to receive IP, remain in the study, or be withdrawn immediately.

The following are prohibited throughout the study: immunomodulatory medications (eg, IVIG, routine systemic corticosteroids, rituximab), emicizumab, aPCC. Bypassing agent therapy is not permitted at any time for participant without inhibitor.

The use of antifibrinolytic agents or medications known to influence platelet function (eg, aspirin, certain non-steroidal anti-inflammatory drugs (NSAIDs) or certain traditional Chinese medicines (TCMs)) within 5 days before initial study drug administration through Day 42 is prohibited.

6.4.2. Treatment(s) for Bleeding Episodes

Bleeding episodes that occur during this study may be treated (on-demand) with hemostatic therapy (recommend intravenous factor products for participants without inhibitors; rFVIIa bypass agent therapy at approximately 90 μg/kg and not to exceed a dosing frequency of every 2 hours for participants with inhibitors; or PCC at the lowest effective dose, in accordance with the Product Prescribing Information) as deemed appropriate by the investigator. The specific treatment with hemostatic therapy is at the discretion of the subject/caregiver/investigator, but all doses of hemostatic therapy taken after signing of informed consent will be documented as concomitant medications or concomitant treatments.

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 the initial administration of PF-06741086 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.

If a participant experiences a bleeding episode during the PK assessment period following administration of PF-06741086, the participant is to be stabilized utilizing the Factor VIII or Factor IX treatment regimen at the lowest effective dose according to the approved Product Prescribing Information, or rFVIIa bypass agent therapy at approximately 90 μg/kg and not to exceed a dosing frequency of every 2 hours, or PCC at the lowest effective dose, in accordance with the Product Prescribing Information, and protocol specified observations and procedures should proceed to completion.

If a participant experiences a bleeding episode after Day 28 following the initial administration of PF-06741086, the participant is to be stabilized utilizing the participant's usual hemostatic treatment regimen.

Treatment with aPCC or other plasma product (eg: Fresh frozen plasma or cyoprecipitate) 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 suitable hemostatic medication.

The use of hemostatic medications for bleeding episodes as specifically outlined in this Section (6.4.2) is not considered to be a protocol violation.

6.5. Dose Modification

Not Applicable.

6.6. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

7.2. Participant Discontinuation/Withdrawal From the Study

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;

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA (visit Day 7) 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 termination 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 (see Section 7.2.1) 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.

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.

The investigator should inquire about the reason for withdrawal, request that the participant return for a final visit, if applicable, and follow-up with the participant regarding any unresolved adverse events (AEs).

It may be appropriate for the participant to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Participants should be questioned regarding their reason for withdrawal. At the early withdrawal visit, every effort must be made to complete the following assessments:
Brief physical examination, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;

- Assess heart rate, respiration rate, temperature and supine blood pressure;
- Single 12-lead ECG measurement (if ECG is abnormal, collect triplicate ECG);
- Obtain blood and urine samples for the following laboratory tests;
- Hematology (details in Table 6);
- Serum chemistry (details in Table 6);
- PT/INR;
- APTT;
- Anti-thrombin III;
- Fibrinogen;
- Cardiac Troponin I (only if withdrawal is prior to CRU discharge/Day 7);
- TFPI (total and free) levels;
- Thrombin Generation;
- Prothrombin fragment 1 + 2;
- D-dimer;
- Dilute prothrombin time (dPT);
- Urinalysis;
- Pharmacokinetic (PK) analysis;
- Immunogenicity (ADA, NAb).

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.

7.2.1. Withdrawal of Consent:

Participants who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified followup procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her 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 investigational product 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 they repeatedly fail 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, they will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific 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.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 289.2 mL. Table 3 reflects approximate sample volumes needed for each measured endpoint. 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 during the study does not exceed 550 mL during any period of 30 consecutive days.

Table 3. Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow -Up	
Safety Labs:					**67**
FVIII or FIX activity	2.7	1	1		**5.4**
FVIII or FIX inhibitor[a]	2.7	1			**2.7**
Serum chemistry (with Lipid profile[a])	4	1	3	0	**16**
Hematology	2	1	3	0	**8**
Serology (HbsAg, HBc Ab, HCV Ab, and HIV)[a]	5	1	0	0	**5**
APTT, PT/INR, Fibrinogen, Anti-thrombin III	2.7 (combined)	1	3	3	**18.9**
Cardiac Troponin I	3	0	3	0	**9**
Other Screening [a]:					**10**
Protein C activity, protein S level,	5	1	0	0	**5**
Factor V Leiden mutation, Prothrombin 20210 mutation	5	1	0	0	**5**
PK: PF-06741086 concentration	4.5	0	8	3	**49.5**
Immunogenicity: (ADA, NAb)	9.0	0	1	3	**36.0**
PD biomarkers:					**128.7**
TFPI (total and free) levels	2.7	0	8	3	**29.7**
TGA	2.7	0	8	3	**29.7**
PF1+2, dPT	4.5 (combined)	0	8	3	**49.5**
D-dimer	1.8	0	8	3	**19.8**
TOTAL					**289.2**

[a] at Screening only.

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed, if applicable.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

- Oral 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 oral 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

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

- At each time point at which triplicate ECG are required (ie, when single ECG is abnormal or when troponin I is abnormal), 3 individual ECG tracings should be obtained approximately 2-4 minutes apart.

Single 12-lead ECGs are performed for all participants in a supine position. If a single time point ECG is abnormal (see Appendix 7 for examples of abnormal results), then a triplicate ECG is required. When done in triplicate, ECGs will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected at pre-dose Day1 will serve as each participant's baseline value.

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.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the 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. 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 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, as defined in Appendix 2, must be conducted in accordance with the 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.

Any remaining serum/plasma from samples collected for clinical safety labs at baseline and at all times post-dosing may be retained and stored for the duration of the study.

8.2.5. Injection Site Reaction

Injection site reactions will be assessed after single dose of PF-06741086 and according to the Schedule of Activities. Injection site reactions will be measured using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.[13] These measurements will be categorized by CTCAE Grades 1-5 (Table 4).

Table 4. 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.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

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 investigational product), through and including a minimum of 42 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, and Pfizer concurs with that assessment.

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 definitively 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 AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from 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 8.2.1, 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.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs 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 and/or SAEs. Open ended and nonleading 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.

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 an 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, institutional review boards (IRBs)/ethics committees (ECs), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until 28 days after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within [24 hours] of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

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 inhalation or 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.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported 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 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 is 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 disease-related events (DREs) are common in participants with hemophilia A or B and can be serious/life threatening:

- Bleeding, pain, swelling, or decreased range of motion due to a bleed

Certain events, due to the participant's hemophilia, will be recorded as a DRE. Investigators

should determine if an event is expected because of the participant's hemophilia. But bleeding or bruising, not due to paticipants' hemophilia, should be recorded as an AE, not a DRE. Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the SAE CRF page in the participant's CRF within 24 hours.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.9. Medical Device Deficiencies

Medical devices are being provided for use in this study as a prefilled syringe for the purposes of 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 8.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.1 through 8.3.4 and Appendix 3 of the protocol.

8.3.9.1. Time Period for Detecting Medical Device Incidents

Medical device deficiencies 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.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such incident 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 8.

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 incident.

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 Sponsor

Device deficiencies will be reported to the sponsor within 1 day after the investigator determines that the event meets the protocol definition of a medical device deficiency. Information will be provided to the sponsor as described in the IP Manual.

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 Section 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 investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product 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 investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study 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 nonserious, 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 immediately.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer).

3. Obtain 2 blood samples (7 days apart) for pharmacokinetic (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 an 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

8.5.1. Analysis of PK PF-06741086 Concentration

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

During all study periods, blood samples (4.5 mL) to provide approximately 2 mL plasma for PK analysis will be collected into appropriately labeled tubes containing sodium citrate at times

specified in the Schedule of Activities. Instructions for the collection and handling of biological samples will be provided in the laboratory 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 samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

Samples will be used to evaluate the PK of PF-06741086. Each plasma sample will be divided into 2 aliquots (1 for routine PK testing, 1 as back up). CCI [redacted]

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/EC 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.

8.4.2 Analysis of Anti-PF-06741086 Antibodies and Neutralizing 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 antibodies (ADA) and neutralizing antibodies (NAb) to PF-06741086 into appropriately labeled tubes containing sodium citrate at times

specified in the Schedule of Activities. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

CCI [redacted]

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. CCI [redacted]

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/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

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, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and data collection tool (eg, CRF).

CCI [redacted]

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

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 dPT) will be summarized for all participants for each of the study days samples are collected. CCI [redacted]

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. 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 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. Each plasma sample will be divided into 2 aliquots of approximately 500 µL each (1 for routine testing, 1 as back up). 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 (PF1+2) and Dilute Prothrombin Time (dPT)

Blood samples of approximately 4.5 mL (combined for PF1+2 and dPT) will be collected into appropriately labeled tubes containing sodium citrate to provide approximately 1.0 mL plasma for PF1+2 analysis and approximately 1.0 mL plasma for dPT 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. D-dimer

Blood samples of approximately 1.8 mL will be collected into appropriately labeled tubes containing sodium citrate to provide approximately 900 µL plasma for 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.

8.7. Genetics

8.7.1. Specified Genetics

A 5 mL blood sample for DNA isolation will be collected. DNA samples will be analyzed for the purpose of assessing Factor V Leiden mutation and prothrombin 20210 mutation only at screening. 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

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

8.8.1. Specified Gene Expression (RNA) Research

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

8.8.2. Specified Protein Research

Specified protein research is not included in this study.

8.8.3. Specified Metabolomic Research

Specified metabolomic research is not included in this study.

8.8.4. Banked Biospecimens for Biomarkers

Banked biospecimen collection is not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

There are no statistical hypotheses and estimands are not applicable.

9.2. Sample Size Determination

Sample size of 6 is not determined based on statistical considerations. The size of 6 is based on CCI [redacted] the purpose of getting preliminary data on Chinese patients CCI [redacted]

9.3. Populations for Analysis

All safety analyses will be performed in Safety Analysis Set which is defined as all participants enrolled in this study who has also taken at least 1 dose of the study drug.

Population	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.
Safety	All participants enrolled in this study who receive at least 1 dose of the study drug.
PK concentration	All participants treated who have at least 1 concentration.
PK parameter	All participants treated who have at least 1 of the PK parameters .
PD parameter	All participants treated who have at least 1 of the PD parameters.

9.4. Statistical Analyses

Descriptive analyses will be performed.

9.4.1. Pharmacokinetic Analysis

9.4.1.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

PK parameters of PF-06741086 following single dose administration will be derived from the concentration-time profiles as shown below in Table 5.

Table 5. Derivation of PF-06741086 Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear

		regression of the log-linear concentration-time curve.
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}	Area under the plasma concentration-time profile from time zero extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis.
CL/F	Apparent clearance	$Dose/AUC_{inf}$
V_z/F	Apparent volume of distribution	$Dose/ (AUC_{inf}*k_{el})$

Actual PK sampling times will be used in the derivation of PK parameters.

9.4.2. Pharmacodynamic Analysis

The PD endpoints include TFPI (total and free), dPT, PF1+2, D-dimer, and thrombin generation (parameters may include lag time, peak thrombin generation, and endogenous thrombin generation potential). These PD endpoints will be listed and summarized descriptively by sampling time.

Maximum change from baseline and area under effect curve for change from baseline PD values may be summarized if data allow.

Parameter	Definition	Method of Determination
Max_{Eff}	Maximum PD change from baseline	Observed directly from data
AUEC	Area under the PD change from baseline-time profile from time zero to Day 28	Linear/Linear trapezoidal method

PK and PD data from this study will also be included in separate population PK and PK/PD analyses. The population PK and PK/PD analyses will be presented separately from the main CSR.

9.5. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, blood pressure (BP), pulse rate, weight, and safety laboratory data (including chemistry, hematology, PT/INR, APTT, urinalysis, fibrinogen, anti-thrombin III activity, and cardiac troponin I) will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Immunogenicity (ADA, NAb) results will be listed (including titers) by timepoint.

9.5.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTc Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

If more than 1 ECG is collected at a nominal time after dose administration (for example, triplicate ECGs), the mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTcF value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec.

Changes from baseline will be defined as the change between the post dose QTcF value and the average of the time -matched baseline triplicate values on Day 1, or the average of the pre-dose triplicate values on Day 1.

9.6. Interim Analyses

No interim analyses will be performed. As this is an open label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling and supporting clinical development.

9.6.1. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

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, investigator's brochure (IB), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

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 subinvestigators 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/her 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 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/EC 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/her 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/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC 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 or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her 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 reconsented to the most current version of the ICD(s) during their participation in the study.

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

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 and/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 data sets 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 or her 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.

10.1.5. 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), and/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 patients) that evaluate the safety and/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 European Union (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 European Union 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.

10.1.6. 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 and/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/EC 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 onsite 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 as 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 the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the 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 the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 site.

Data reported on the CRF or entered in the electronic CRF (eCRF) 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 monitoring plan.

10.1.8. 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 the contract research organization (CRO) if requested to do so by the responsible IRB/EC 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/EC 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.

10.1.9. 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 1 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 submits 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 for 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.

10.1.10. 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. The contact card contains, at a minimum, protocol and investigational product identifiers, participant 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. The contact number is not intended for use by the participant directly, and if a participant calls that number, they will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 6. Protocol Required- Safety Laboratory Assessments

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein Lipid profile[b]	Ph Glucose Protein Blood Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy& Culture[a]	HBsAg[b] HBcAb[b] HCVAb[b] HIV[b] CD4 cell count[b] Anti-thrombin III Protein C activity[b] Protein S level[b] Factor V Leiden mutation[b] Prothrombin 20210 Mutation[b] PT/INR APTT Fibrinogen Cardiac Troponin I Factor VIII activity[c] Factor IX activity[c] Factor VIII and Factor IX inhibitor [b] urine drug screening[d]
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase Total bile acids GGT PT/INR		

Abbreviations: Abs = absolute; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; HbsAg= hepatitis B surface antigen; HBc Ab=hepatitis B core antibody; HCV Ab=hepatitis C virus antibody;HIV=human immunodeficiency virus; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

a. Only if urinalysis is positive for blood, protein, leukocyte or nitrites.
b. At Screening only.
c. At Screening, Day 1 and Day 7 only
d. At Screening and Day -1 only. Minimum requirement for drug screening includes: cocaine, tetrahydrocannabinol(THC), opiates/opioids, benzodiazepines and amphetamines.

Investigators must document their review of each laboratory safety report.

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 Meeting the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
 	
  ◦ Is associated with accompanying symptoms;
 	
  ◦ Requires additional diagnostic testing or medical/surgical intervention;
 	
  ◦ 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 and/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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
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. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but 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.
- 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.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the investigational product 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
Nonserious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and exposure during pregnancy [EDP] supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

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/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/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:

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.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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.
- 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 investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/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 investigational product caused the event, then the event will be handled as "related to investigational product" 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 healthcare 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 completed CRF.
- 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) 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.

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

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

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 while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed 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 and/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: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

  Samples for specified genetic analysis (see Section 8.7.1) will not be stored beyond the completion of this study.

10.6. Appendix 6: 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 (D

ILI). 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) and/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 laboratory 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, gammaglutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase at the discretion of the investigator. 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 and/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.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)

- Marked sinus bradycardia (rate <40 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 (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

- QTc F 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 patients 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 patients 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 (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >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 Serious Adverse Events
• 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.

10.8. Appendix 8: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

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 (see Section 6.1.1) for the list of sponsor medical devices).

10.8.1. Definition of AE and ADE

AE and ADE 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 for study participants, users, and other persons. This definition also includes events considered related to procedures for study participants only. • 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.

10.8.2. Definition of SAE, SADE, and Unanticipated Serious Adverse Device Effect

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, 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: • 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. • A permanent impairment of a body structure or a body function. • 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. • 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
• An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
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.

10.8.3. 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 labeling.

10.8.4. Recording/Reporting and Follow-up of AEs and/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 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, and/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.
    - 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:

- 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, and/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 and/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 and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/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.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

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.

10.8.6. Reporting of SADEs

SADE Reporting to Pfizer Safety

NOTE: There are additional reporting obligations for medical device incidents that are potentially related to SAEs 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.

10.9. Appendix 9: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ABR	annualized bleeding rate
Abs	Absolute
ADA	antidrug antibodies
ADCC	antibody-dependent cell-mediated cytotoxicity
ADE	adverse device effect
AE	adverse event
ALB	albumin
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATIII	anti-thrombin III
AUC	area under the curve
AUC_{inf}	area under the concentration time curve from time 0 to infinity
AUC_{last}	area under the concentration time curve from time 0 to the time of the last quantifiable concentration
AUC_t	area under the concentration-time curve from time 0 to time t, where t can have a numerical value
AUEC	area under the PD change from baseline time profile from time zero to Day 28
BID	Twice a day
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CDC	Complement dependent cytotoxicity
CDE	Center for Drug Evaluation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum observed concentration
CNS	central nervous systems
CL/F	apparent clearance
CO_2	carbon dioxide (bicarbonate)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	clinical study report
CT	clinical trial

Abbreviation	Term
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	cardiac troponin I
CV	cardiovascular
%CV	geometric percent coefficient of variation
DILI	drug induced liver injury
DMC	data monitoring committee
dPT	dilute prothrombin time
DRE	disease-related event
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FcR	Fc receptor
Fg	fibrinogen
FIH	first in human
FIP	first in patient
FVIIa	factor-activated coagulation factor VII
FIX	coagulation factor IX
FXa	activated coagulation factor IX
rFVIIa	recombinant activated coagulation factor VII
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
eGFR	Estimated glomerular filtration rate
GGT	gamma-glutamyl transferase
GLOB	globulin
GLP	Good Laboratory Practice
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
K_{el}	the terminal phase rate constant calculated by a linear regression of the loglinear concentration time curve.
K1	Kunitz domain 1
K2	Kunitz domain 2
hr	hours
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification

Abbreviation	Term
IFN- γ	Interferon gamma
IgG1	immunoglobulin G isotype, subclass 1
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
IL-6	Interleukin-6
IP manual	investigational product manual
ISO	International Organization for Standardization
IRB	institutional review board
IV	intravenous
IVIG	IV immunoglobulin
LFT	liver function test
LLN	lower limit of normal
Max_{Eff}	Maximum PD change from baseline
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
min	minutes
msec	millisecond
N/A	not applicable
NAb	neutralizing antibodies
NIMP	noninvestigational medicinal product
NMPA	National Medical Products Administration
NOAEL	no-observed-adverse-effect level
NSAIDs	non-steroidal anti-inflammatory drugs
PCC	prothrombin complex concentrate
PCD	primary completion date
PD	pharmacodynamic(s)
PF1+2	prothrombin fragment 1+2
PK	pharmacokinetic(s)
PT	prothrombin time
PWH	people with hemophilia
PVC	premature ventricular contraction/complex
QW	once weekly
QTc	corrected QT interval
QTcF	corrected QT interval (Fridericia method)
QoL	quality of life
QW	once weekly
RBC	red blood cell
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous
SoA	schedule of activities
SOP	standard operating procedure
SPR	Surface Plasmon Resonance
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	apparent terminal half-life
Tbili	total bilirubin
TCMs	traditional Chinese medicine
TEAE	treatment-emergent adverse events
TEG	thromboelastography
TF	tissue factor
TGA	thrombin generation assays
THC	tetrahydrocannabinol
TFPI	tissue factor pathway inhibitor
T_{max}	time to reach maximum concentration
TNF α	Tumor necrosis factor α
TK	toxicokinetic
ULN	upper limit of normal
US	United States
WBC	white blood cell
WFH	World Federation of Hemophilia

10.10. Appendix 10: Alternative Measures 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).

10.10.1. Eligibility

While SARSCoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2.

10.10.2. Telehealth Visits

In the event that in-clinic study visits can not 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 (e.g., 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 10.3, Appendix 3).
- Confirm that the participant is adhering to the contraception method(s) required in the protocol.
- Review bleeding episodes and factor or bypass infusions.

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

10.10.3. Alternative Facilities for Safety Assessments

10.10.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology
- Serum chemistry
- APTT,PT/INR,Fg
- Anti-thrombin III;
- Cardiac Troponin I;
- Urinalysis;

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

10.10.3.2. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.10.4. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

10.10.5. 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:

- Physical exam/brief physical exam
- All protocol required lab draws
- Weight and vital signs (eg, body temperature, BP, pulse rate, respiratory rate).

10.10.6. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

11. REFERENCES

1. Srivastava A, Brewer AK, Mauser-Bunschoten EP et al. Guidelines for the management of hemophilia. Haemophilia 2013; 19: e1–47
2. 2017 Global annual survey report World Federation of Hemophilia (WFH)
3. China Statistical Yearbook 2011
4. Sun J et al.The demographics, treatment characteristics and quality of life of adult people with haemophilia in China - results from the HERO study. Haemophilia. (2017)
5. Poon MC, Luke KH. Haemophilia care in China: achievements of a decade of World Federation of Hemophilia treatment centre twinning activities. Haemophilia 2008;14(5):879-88
6. MC Ozelo, MA Matta, R Yang Meeting the challenges of haemophilia care and patient support in China and Brazil Haemophilia, 2012
7. Runhui Wu et al The benefit of low dose prophylaxis in the treatment of hemophilia: a focus on China Expert review of hematology 2017;10:995-1004
8. Berntorp E, Shapiro AD. Modern haemophilia care. Lancet. 2012;379(9824):1447-56.
9. Astermark J. Overview of inhibitors. Semin Hematol. 2006;43(2 Suppl 4):S3-7.
10. Maroney SA, Ellery PE, Wood JP, et al. Comparison of the inhibitory activities of human tissue factor pathway inhibitor (TFPI)alpha and TFPIbeta. J Thromb Haemost.2013;11(5):911-8.
11. Knappe S, Gorczyca ME, Jilma B, et al. Plasmatic tissue factor pathway inhibitor is a major determinant of clotting in factor VIII inhibited plasma or blood. Thromb Haemost. 2013;109(3):450-7.
12. Dahm A, Van Hylckama Vlieg A, Bendz B, et al. Low levels of tissue factor pathway inhibitor (TFPI) increase the risk of venous thrombosis. Blood. 2003;101(11):4387-92.
13. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events. Version 5.0. 27 November 2017

Document Approval Record

Document Name:	PF-06741086_Protocol Amendment_B7841010_Amendment 1
Document Title:	B7841010 protocol amendment 1

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Apr-2021 06:44:59	Author Approval