A MULTICENTER, OPEN-LABEL, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF SUBCUTANEOUS OR INTRAVENOUS PF-06741086 IN SUBJECTS WITH SEVERE HEMOPHILIA

Compound:	PF-06741086
Compound Name:	Not applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2016-001885-27
Protocol Number:	B7841002
Phase:	1b/2

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 4	02 Oct 2017	**Title** • Removed "AND" from "AND/OR" to conform to previous amendment that removed a combination subcutaneous and intravenous dose. **General Changes Throughout Protocol** • Editorial changes to fix titles, headers, grammar and typographical errors. **Schedule of Activities** • Revised window for Day 2, Day 4, Day 30 and Day 33 visits to ± 1 day to allow for scheduling flexibility. • Added reference to FVIII and FIX inhibitor levels (to allow for inclusion of subjects with inhibitors) and CD4 cell count (editorial change). **Protocol Summary** • Added language allowing for the inclusion of subjects with inhibitors against FVIII or FIX. • Added language excluding subjects with inhibitors who must use APCC (FEIBA) for bypass therapy and cannot substitute treatment with FVIIa (eptacog alfa [activated]) at approximately 90 µg/kg. **Section 1.2.1. Nonclinical Pharmacology and Pharmacokinetics** • Added a summary of the nonclinical combination pharmacology data supporting the combination of PF-06741086 and FVIIa (eptacog alfa

Document	Version Date	Summary of Changes
		[activated]). **Section 1.2.2. Nonclinical Toxicology** • Added a summary of the nonclinical toxicology study data supporting 6 months of treatment with of PF-06741086. **Section 1.3.2. Study Rationale** • Added language allowing for the inclusion of subjects with inhibitors **Section 1.3.4. Summary of Risk/Benefit** • Added language allowing for the inclusion of subjects with inhibitors and the use of concomitant bypass agent therapy during PF-06741086 treatment. **Section 2.1. Objectives** • Added language allowing for the inclusion of subjects with inhibitors against FVIII or FIX. **Section 3. Study Design** • Updated Figure 1 – Dose Progression Scheme to make it easier to understand. **Section 3.1. Planned Number of Subjects** • Added language stating that subjects with inhibitors will be enrolled into cohorts currently open for enrollment. **Section 3.3. Dose Escalation and Stopping Rules** • Revised language to clarify dose progression definition, in order to

Document	Version Date	Summary of Changes
		allow for a cohort at a previously studied dose to be evaluated if necessary. **Section 4.1. Inclusion Criteria** • Revised Inclusion Criterion #4 to remove language prohibiting subjects with inhibitors against Factor VIII or Factor IX. • Added Inclusion Criterion #5 to establish criteria for subjects with inhibitors to FVIII or FIX. • Revised Inclusion Criterion #6 to add language on washout requirements for bypass agent therapy. **Section 4.2. Exclusion Criteria** • Removed Exclusion Criterion #5 which prohibited subjects with inhibitors (≥ 0.6 Bethesda Units [BU]) from eligibility. • Revised Exclusion Criterion #6 to remove the exclusion of FVIIa (eptacog alfa [activated]) subjects, and revise the exclusion of APCC treated subjects to those subjects who cannot substitute treatment with factor VIIa (at a dose level of approximately 90 µg/kg) for the duration of the study. **Section 4.3. Randomization Criteria** • Added language on washout requirements prior to Day 1 for FVIIa bypass agent therapy. **Section 5. Study Treatments** • CCI [redacted]

[redacted]

Document	Version Date	Summary of Changes
		CCI [redacted] **Section 5.3.1. Dosage Form(s) and Packaging** • CCI [redacted] **Section 5.7.1. Prohibited Medications** • Added language on washout requirements for bypass agent therapy. • Revised language regarding prohibitions against the use of FVIIa bypass therapy, including restricting use to approximately 90 µg/kg, and added language stating that subjects using APCC therapy, who cannot switch to FVIIa therapy, are not eligible for the study. **Section 5.7.2. Treatment for Acute Bleeding Episodes** • Added language allowing for FVIIa bypass therapy at approximately 90 µg/kg for acute bleeding episodes. **Section 6.1. Screening** • Added a review of inhibitor history and a review of bypass agent therapy use to Screening activities. • Added reference to CD4 cell count. **Section 6.2.1. Day 1 Visit** • Added a review of bypass agent therapy use to Day 1 activities.

Document	Version Date	Summary of Changes
		Section 6.2.2. Day 2 (±1 day) and Day 4 Visit (±1 day) • Revised window for Day 2 and Day 4, to ± 1 day to allow for scheduling flexibility. **Section 6.2.4. Day 30 (±1 day) and Day 33 Visit (±1 day)** • Revised window for Day 2 and Day 4, to ± 1 day to allow for scheduling flexibility. **Section 7.1.1 Laboratory Tests** • Added reference to FVIII and FIX inhibitor levels (to allow for inclusion of subjects with inhibitors) and CD4 cell count (editorial change). **Section 7.2.1. Hemophilic Bleeding Episodes** • Added language to include the use of bypass agent therapy for assessing bleeding episodes. **Section 7.2.1. Treatment of Bleeding Episodes** • Added language to include FVIIa bypass agent therapy as a treatment of bleeding episodes. **Section 9.2.1. Analysis of the Efficacy Endpoint** • Added language to specifiy analyses for inhibitor subjects.
Amendment 3	12 December 2016	**Section 3.3. Dose Escalation and Stopping Rules** • Removed language in dose escalation

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		section that maintained subjectivity in stopping rules. Objective set of criteria for stopping rules is now listed in Section 3.3. • Added reference to the NIAID DMID criteria for adverse event grading for dose escalation criteria. Grade 3 adverse events will all qualify as dose-limiting toxicities, as specified in Appendix 2. • Deleted statement on analysis of thrombotic events by background of prothrombotic conditions, as these subjects are no longer eligible for the study. • Removed all references to investigator attribution of causality. • Added objective criterion for dose-escalation stopping rules based on tolerability. • Added criteria and plans for dose modifications for individual subjects with our without a dose-limiting toxicity. **Section 4.1. Inclusion Criteria** • Revised Inclusion Criterion #2 to state that only adult subjects (18 to 65 years of age) are eligible for the study. **Section 4.2. Exclusion Criteria** • Added Exclusion Criterion #4 to state that subjects with pro-thrombotic conditions are excluded from the study**.** **Appendix 2** • Changed title of Appendix 2 to "Criteria for Dose Limiting Toxicity" • Added severe/Grade3 TEAE criterion as a

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		dose limiting toxicity. • Added reference to the NIAID DMID criteria for toxicity grading.
Amendment 2	02 November 2016	**General Changes Throughout Protocol** • Removed "and/or" clause for routes of administration as subjects will not be administered via both IV and SC routes of administration. • Editorial changes to fix titles, headers, grammar and typographical errors. **Protocol Title Page** • Added US IND # to protocol. **Protocol Summary** • Added requirement for episodic (on-demand) treatment for inclusion to the study. • Removed option for self-administration by subjects for SC cohorts and specified visits for SC cohorts. • Added text stating that adverse events will be graded by the WHO scale. **Schedule of Activities:** **Table 1** • Footnote (i): deleted reference to an IV loading dose and SC doses. This will not be administered in this study. • Footnote (j): deleted reference to recording information in the subject diary on self-administration. **Table 2**

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		• Revised table headers to remove references to treatment self-administration and specify visits for SC cohorts. • Footnote (h): revised text to mimic Footnote (j) in Table 1. • Revised inaccurate reference to Footnote (g) in the header row of Table 2 to the correct Footnote (f). **Section 1.2.1. Nonclinical Pharmacology** • Updated exposure multiples based on data from completed first-in-human study. **Section 1.3.1.1. Overall Safety** • Added a brief statement on the final safety data from the B7841001 first-in-human study. **Section 1.3.1.2. Plasma Pharmacokinetics of PF-06741086 Following Administration of Single IV and SC Doses of PF-06741086** • Added a new section to detail final PK data from the B7841001 first-in-human study. **Section 1.3.1.3. Pharmacodynamics of PF-06741086 Following Administration of Single IV and SC Doses of PF-06741086** • Added a new section to detail final PD data from the B7841001 first-in-human study. **Section 1.3.3. Dose Rationale** • Added a new section (1.3.3.1 Starting Dose) to detail justification for the 300 mg starting dose. • Revised nominal doses planned for

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		Cohorts 2 through 4 added to new section (1.3.3.2 Dose Progression). Starting dose and route of administration for Cohort 1 did not change. • Table 4: updated PK projections for the revised nominal doses in Section 1.3.3. **Section 3. Study Design** • Figure 1 was updated to include revised nominal doses planned for Cohorts 2 through 4. The title was revised from "Dose Escalation Scheme" to "Dose Progression Scheme" as planned doses may not be escalating. • Updated bullet list below Figure 1 to include revised nominal doses planned for Cohorts 2 through 4. Removed reference to "dose escalating fashion" as planned doses may not be escalating. **Section 3.2. Study Duration** • Removed option for self-administration for SC cohorts and specified visits for SC cohorts. **Section 3.3. Dose Escalation and Stopping Rules** • Removed the requirement for "clinical significance" from all stopping criteria, to make the criteria less subjective. • Added text indicating that vessel occlusion secondary to venous catheter placement may be excluded from the stopping criteria. Also added

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		text that thrombotic adverse events will be evaluated based against baseline pro-thrombotic risk factors. • Added a stopping criterion for the review of all adverse events, without regard to organ class or relationship to treatment. **Section 4.1. Inclusion Criteria** • Inclusion Criterion #5: criterion was revised to state that only patients currently treated with episodic (on-demand) factor replacement therapy are eligible for this study. **Section 4.4. Lifestyle Guidelines** • Added text indicating that contraception requirements may be extended if new data from B7841002 warrant such a change. **Section 5.2. Subject Compliance** • Removed option for self-administration for SC cohorts and specified visits for SC cohorts. **Section 5.3.2. Preparation and Dispensing** • Removed option for self-administration. **Section 5.4. Administration** • Removed option for self-administration. **Section 5.5. Investigational Product Storage** • Removed option for

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		self-administration. • Revised section on temperature monitoring to conform to Sponsor requirements for active monitoring. **Section 5.6. Investigational Product Accountability** • Removed option for self-administration. **Section 5.7. Concomitant Treatment(s)** • Added a requirement for investigator to contact the Sponsor medical monitor to review concomitant treatment in the case of emergency or unplanned surgery. **Section 5.7.1. Prohibited Medications** • Added text indicating that additional washout time may be necessary depending on the coagulation factor product in use. **Section 6.2.3. Day 8 (±1 day), Day 15 (±2 days), Day 22 (±2 days) and Day 29 (±2 days) at Clinic Visits** • Removed reference to IV loading dose as there will not be an IV and SC route of administration. • Added a bullet to indicate Day 29 administration of IP for IV cohorts only, to conform with the Schedule of Activities. **Section 6.2.5. Day 36 (±2 days), Day 43 (±2 days) and Day 50 (±2 days) at Clinic Visits** • Removed reference to IV loading dose

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		as there will not be an IV and SC route of administration. • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary. **Section 6.2.6. Day 57 (±2 days) at Clinic Visit** • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary. **Section 6.2.7. Day 64 (±2 days), Day 71 (±2 days) and Day 78 (±2 days) at Clinic Visits** • Removed reference to IV loading dose as there will not be an IV and SC route of administration. • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary. **Section 6.2.8. Day 85 (±2 days) at Clinic Visit** • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary. **Section 6.3.1. Day 113 (±7 days) at Clinic Visit** • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary.

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		Section 6.4. Subject Withdrawal • Removed option for self-administration. Removed requirement for collection of self-administration on subject diary. **Appendix 1** • Added Appendix 1 to list thrombotic adverse events that would qualify for stopping criteria.
Amendment 1	09 September 2016	**Protocol Title Page** • Added EudraCT # to protocol. **Section 4.1 – Inclusion criteria** • Revised inclusion criterion #2 to restrict subjects from ≥12 and <18 years of age to cohorts at a dose level and route of administration previously studied which has not met the protocol safety criteria for termination of dose escalation. This change was implemented to comply with regulatory requests in the EU.
Original protocol	09 April 2016	Not applicable

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

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PROTOCOL SUMMARY

Study B7841002 is a Phase 1b/2, open-label, multiple ascending dose clinical study in subjects with severe hemophilia A or B, with or without inhibitors to Factor VIII (FVIII) or Factor IX (FIX). This study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of multiple subcutaneous (SC) or intravenous (IV) doses of PF-06741086, a monoclonal antibody that targets tissue factor pathway inhibitor (TFPI).

TFPI is an antagonist of the extrinsic coagulation pathway. PF-06741086, through its neutralization of TFPI, is expected to increase coagulation activity. Study B7841002 will assess the effect of PF-06741086 on various measures of coagulation, including the number of acute bleeding episodes during a 3-month treatment period as a measure of prophylaxis efficacy. Satisfactory safety, tolerability, PK, PD and efficacy data from this study are intended to support the development of PF-06741086 as a monotherapy for prophylactic treatment to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B with or without inhibitors.

Subjects with severe hemophilia A or B (defined by factor VIII or factor IX activity ≤1%), including subjects with inhibitors to factor VIII or factor IX (positive inhibitor test result [above the upper limit of normal]), who receive bypass agents as primary treatment for bleeding episodes) will be recruited into B7841002. Subjects with inhibitors who are currently treated with activated prothrombin complex concentrate (APCC, eg, FEIBA) and cannot substitute treatment with recombinant factor VIIa (rFVIIa, eptacog alfa [activated]) as their standard of care for treatment of acute bleeding episodes (at a dose level of approximately 90 µg/kg) for the duration of the study are not eligible. Subjects must be on an episodic (on-demand) treatment regimen at the time of study enrollment and also have a documented history of at least 6 acute bleeding episodes in the 6 months prior to study enrollment. Subjects must washout from any factor replacement or *bypass* agent therapy prior to screening and prior to study treatment.

Subjects who meet the eligibility criteria will be assigned to a PF-06741086 treatment cohort, defined by a specific dose level, dose frequency and route of administration. Subjects will be treated with PF-06741086 for up to 3 months, with a maximum of 5 months expected for overall study participation. Approximately 24 subjects (4 treatment cohorts with 6 subjects per cohort) are planned to be treated. The planned number of subjects, cohorts, dose levels, dose frequencies and route of administration may change depending on the results from each cohort dosed in the study.

Subjects will be required to attend weekly clinic visits during the first month of the study (Day 1 to Day 29). An additional two clinic visits at Day 2 and Day 4 will be required for PK/PD blood draws. Through Day 29 (at a minimum), data will be reviewed to determine if PF-06741086 is safe and well tolerated. Dosing of subjects in any cohort may be stopped if the B7841002 protocol-specified stopping criteria are met, or if available data indicate that the current dose is not safe and well tolerated. If available safety, tolerability and PK data through Day 29 are permissive for dose escalation, a cohort at a higher dose level (SC or IV administration) may be opened for enrollment. Alternatively, a cohort at a lower dose level may be opened if data are supportive.

In addition, if the dose level under review is safe and well tolerated through Day 29, treatment will continue for the subjects in that respective cohort during the subsequent 2 months (Day 30 to Day 85). During this period, clinic visits at Day 30 and Day 33 will be required for PK/PD blood draws for all cohorts. Subjects in the SC cohorts will receive treatment on Day 36, Day 43, Day 50, Day 57, Day 64, Day 71, Day 78, follow-up on Day 85, and end-of-study procedures on Day 113. Subjects in the IV cohort will return to the clinic for treatment on Day 57, follow-up on Day 85, and end-of-study procedures on Day 113. Follow-up beyond Day 113 may be required for any subjects that test positive for an anti-drug or neutralizing antibody during the study.

There is no formal statistical hypothesis planned for testing in B7841002. There is no formal sample size calculation informing cohort sample size or overall study sample size. The cohort sample sizes and overall study sample size are based on clinical considerations to balance the need to minimize exposure of study subjects to the test article with the need to provide adequate safety, tolerability, PK, PD and efficacy data at each dose level and/or route of administration. Additional subjects and/or cohorts may be enrolled in the event that the number of dosing cohorts or size of dosing cohorts is increased to fully explore the dose range and/or clinical profile at the respective dose levels.

Safety endpoints will include treatment emergent adverse events (graded by the NIAID DMID severity scale), infusion/injection site reactions, laboratory parameters that may be modulated due to coagulopathy (eg, prothrombin time [PT]/INR, activated partial thromboplastin time [aPTT], fibrinogen, antithrombin III [ATIII], platelet counts) and parameters to screen for possible thrombotic events (eg, cardiac troponin I). PK and PD endpoints include concentrations of PF-06741086 in plasma, non-compartmental PK parameters, measures of target binding by PF-06741086 (ie, TFPI level) or downstream pharmacological activities of TFPI inhibition (ie, dilute PT, thrombin generation, prothrombin fragment 1+2, and D-dimer). Prophylaxis efficacy will be assessed by collecting the number of acute bleeding episodes per subject during the treatment period of 3 months and determining the annualized bleed rate (ABR) for comparison against historical data. These data will be summarized descriptively for each cohort and the overall study.

Demonstration of safety, tolerability and a PK/PD/efficacy profile that is supportive for long-term chronic treatment on an acceptable dosing schedule will allow for progression of PF-06741086 to subsequent investigations in patients with severe hemophilia A or B.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections 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 on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Study Flow Chart – Screening and Treatment Period (Day -34 to Day 29)

Protocol Activity	**Screening**	**Treatment**						
Visit Identifier	**Screening**	**Day 1**	**Day 2 PK/PD Blood Draw**	**Day 4 PK/PD Blood Draw**	**Day 8**	**Day 15**	**Day 22**	**Day 29**
Visit window relative to end of Day 1 IP administration	**Day -34 to Day 0**		**-6 hours/+1 day**	**-6 hours/+ 1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**
Informed consent	X							
Medical history (including hemophiliahistory and bleeding episodes over past 6 months)	X							
Medication history	X	X						
Demography, Height	X							
Physical examination[a]	X	X			X	X	X	X
Weight	X	X						X
Contraception instructions/check[b]	X	X			X	X	X	X
Vital Signs[c]	X	X			X	X	X	X
Urinalysis	X	X			X	X	X	X
ECG[d]	X	X			X	X	X	X
Serum chemistry	X	X			X	X	X	X
Hematology[e]	X	X			X	X	X	X
Factor VIII and Factor IX activity	X	X						

Table 1. Study Flow Chart – Screening and Treatment Period (Day -34 to Day 29)

Protocol Activity	**Screening**	**Treatment**						
Visit Identifier	**Screening**	**Day 1**	**Day 2 PK/PD Blood Draw**	**Day 4 PK/PD Blood Draw**	**Day 8**	**Day 15**	**Day 22**	**Day 29**
Visit window relative to end of Day 1 IP administration	**Day -34 to Day 0**		**-6 hours/+1 day**	**-6 hours/+ 1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**
Factor VIII and Factor IX inhibitor levels (for subjects with a hemophilia history of inhibitor only)	X[k]							
CD4 cell count								
Prothrombin 20210 mutation testing	X							
Factor V Leiden mutation testing	X							
Lipid profile[f]	X							
Protein C activity/Protein S level	X							
Serology: HBs Ag, HBc Ab, HCV Ab and HIV	X							
Banked biospecimens (Prep D1)		X						
TFPI level		X[g]	X	X	X	X	X	X
PT/INR	X	X			X	X	X	X
aPTT	X	X			X	X	X	X
Fibrinogen	X	X			X	X	X	X
Anti-thrombin III	X	X			X	X	X	X
Thrombin Generation (TGA)		X[g]	X	X	X	X	X	X
Prothrombin fragment 1+2 (PF1+2)		X[g]	X	X	X	X	X	X
D-dimer		X[g]	X	X	X	X	X	X
Dilute prothrombin time (dPT)		X[g]	X	X	X	X	X	X
Cardiac Troponin I		X			X	X	X	X
PK blood sampling		X[g]	X	X	X	X	X	X[g]

Table 1. Study Flow Chart – Screening and Treatment Period (Day -34 to Day 29)

Protocol Activity	**Screening**	**Treatment**						
Visit Identifier	**Screening**	**Day 1**	**Day 2 PK/PD Blood Draw**	**Day 4 PK/PD Blood Draw**	**Day 8**	**Day 15**	**Day 22**	**Day 29**
Visit window relative to end of Day 1 IP administration	**Day -34 to Day 0**		**-6 hours/+1 day**	**-6 hours/+ 1 day**	**±1 day**	**±2 days**	**±2 days**	**±2 days**
Immunogenicity (ADA, NAb)		X				X		X
CCI		C				C		C
Inclusion/exclusion criteria review	X	X						
Treatment assignment[h]		X						
Investigational Product administration		X			X[i]	X[i]	X[i]	X
Subject diary[j]		X			X	X	X	X
Collect information on new bleeding episodes	X	→	→	→	→	→	→	→
Monitoring infusion/ injection site reactions		X	→	→	→	→	→	→
Adverse event monitoring	X	→	→	→	→	→	→	→
Concomitant treatments	X	→	→	→	→	→	→	→

Abbreviations: → = ongoing/continuous event; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; 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; IP = investigational product; N/A = not applicable; NAb = neutralizing antibodies; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio; TFPI = tissue factor pathway inhibitor

a. A full physical examination (PE) will be conducted during Screening. On and after Day 1 and at the discretion of the Investigator, limited examinations based on signs and symptoms will be performed, if clinically indicated to assess changes from baseline/previous visits of any ongoing symptoms.
b. Instructions will be provided at Screening and at Follow-up/End of Study visit; contraception check will be performed at other visits. A longer duration of contraception usage may be required if data from B7841002 warrant this change.
c. Vital signs to be assessed include pulse rate, respiratory rate, oral temperature, and supine blood pressure.
d. Triplicate ECG required at Day 1. Single ECG required at additional time points unless ECG is abnormal, in which case a triplicate ECG is required.
e. Differential hematology panel required at Days 1, 29, 85 and 113.
f. Subjects must be fasting for 12 hours prior to blood draw.
g. One sample will be drawn prior to IP administration for both the subcutaneous (SC) and intravenous (IV) routes of administration. For IV administration only, collect a second sample from the arm not used for IV IP administration immediately (0 to 5 minutes) following completion of the IV infusion and line flush.
h. Treatment assignment may occur at any time prior to dosing once subject has met all eligibility criteria.
i. IP is administered at these visits for cohorts with SC administration only.

j. Subject diary dispensed and/or collected. Subject diary is reviewed, including information about study compliance bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. At Day 1, subjects will be provided training with respect to filling out the diary including timing and nature of information to be entered.
k. FVIII and FIX inhibitor levels must be determined by a local laboratory. A positive inhibitor test result will be above the upper limit of normal for the assay. Inhibitor test results from up to 6 months prior to Day 1 may be used to meet this requirement.

Table 2. Study Flowchart – Treatment and Follow-up Period (Day 30 to Day 113)

Protocol Activity	**Treatment**										**Follow-up/End of Study**[f]
Visit Identifier	**Day 30 PK/PD Blood Draw**	**Day 33 PK/PD Blood Draw**	**Day 36 (SC Cohort)**	**Day 43 (SC Cohort)**	**Day 50 (SC Cohort)**	**Day 57**	**Day 64 (SC Cohort)**	**Day 71 (SC Cohort)**	**Day 78 (SC Cohort)**	**Day 85**	**Day 113**
Visit Window relative to end of Day 29 IP administration	**-6 hours/+ 1 day**	**-6 hours/+ 1 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Physical examination[a]						X				X	X
Weight						X				X	X
Contraception instructions/check[b]						X				X	X
Vital Signs[c]						X				X	X
Urinalysis						X				X	X
Serum chemistry						X				X	X
Hematology[d]						X				X	X
TFPI level	X	X				X				X	X
PT/INR						X				X	X
aPTT						X				X	X
Fibrinogen						X				X	X
Thrombin Generation (TGA)	X	X				X				X	X
Prothrombin fragment 1+2 (PF1+2)	X	X				X				X	X
D-dimer	X	X				X				X	X
Dilute prothrombin time (dPT)	X	X				X				X	X
PK blood sampling	X	X				X[e]				X	X
Immunogenicity (ADA, NAb)						X				X	X[f]
CCI [redacted]						C				C	
Investigational Product administration			X[g]	X[g]	X[g]	X	X[g]	X[g]	X[g]		

Table 2. Study Flowchart – Treatment and Follow-up Period (Day 30 to Day 113)

Protocol Activity	Treatment										Follow-up/End of Study[f]
Visit Identifier	**Day 30 PK/PD Blood Draw**	**Day 33 PK/PD Blood Draw**	**Day 36 (SC Cohort)**	**Day 43 (SC Cohort)**	**Day 50 (SC Cohort)**	**Day 57**	**Day 64 (SC Cohort)**	**Day 71 (SC Cohort)**	**Day 78 (SC Cohort)**	**Day 85**	**Day 113**
Visit Window relative to end of Day 29 IP administration	**-6 hours/+ 1 day**	**-6 hours/+ 1 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±2 days**	**±7 days**
Subject diary[h]			X	X	X	X	X	X	X	X	X
Collect information on new bleeding episodes	→	→	→	→	→	→	→	→	→	→	X
Monitoring infusion/ injection site reactions	→	→	→	→	→	→	→	→	→	→	X
Adverse event monitoring	→	→	→	→	→	→	→	→	→	→	X
Concomitant treatment	→	→	→	→	→	→	→	→	→	→	X
Discharge from study											X

Abbreviations: → = ongoing/continuous event; ADA = anti-drug antibodies; aPTT = activated partial thromboplastin time; 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; IP = investigational product; N/A = not applicable; NAb = neutralizing antibodies; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio; TFPI = tissue factor pathway inhibitor

a. On and after Day 1, limited physical 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. Instructions provided at Screening and at Follow-up/End of Study visit, contraception check at other visits. A longer duration of contraception usage may be required if data from B7841002 warrant this change.
c. Vital signs to be assessed include pulse rate, respiratory rate, oral temperature, and supine blood pressure.
d. Differential hematology panel required at Days 1, 29, 85 and 113.
e. One PK sample will be drawn prior to IP administration for both the SC and IV routes of administration. For IV administration only, collect a second sample from the arm not used for IV IP administration immediately (0 to 5 minutes) following completion of the IV infusion and line flush.
f. Subjects with positive ADA or NAb may be required to attend additional, unscheduled follow-up visits following Day 113.
g. IP is administered at these visits for cohorts with SC administration only. IP may be administered by investigator site personnel in a home care or ambulatory clinic setting in countries where it is approved by the respective competent authority and at sites where it is approved by the respective IRB/EC.
h. Subject diary dispensed and/or collected. Subject diary is reviewed, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. At Day 1, subjects will be provided training with respect to filling out the diary including timing and nature of information to be entered.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

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.

Protocol B7841002 is a first-in-patients safety and pharmacology study with PF-06741086. This study will provide the initial clinical assessment of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of PF-06741086 following administration of subcutaneous (SC) or intravenous (IV) doses at ascending dose levels. Data on bleeding events will be collected to evaluate the therapeutic efficacy of PF-06741086. Study B7841002 will also assess the effect of PF-06741086 on various measures of coagulation. Satisfactory safety, tolerability, PK and PD data from this study are intended to support the development of PF-06741086 as a prophylactic treatment in hemophilia.

1.2. Background

The current standard of care for treatment of individuals with hemophilia A or B is replacement of their deficient clotting factor using factor VIII (FVIII) or factor IX (FIX) clotting factor concentrate, respectively.[1] This 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-in-line therapy for prophylaxis against or treatment of hemophilia bleeding episodes.[2] For patients who respond to clotting factor replacement, the IV administration route and frequency of infusion required for effective prophylaxis treatment remains burdensome, and may result in reduced adherence and compromised prophylactic efficacy. As well, venous access for IV administration of clotting factor concentrates is limited in the youngest pediatric patients with hemophilia. In these patients, indwelling central venous catheters are frequently required to assure venous access with the attendant infectious and thrombotic complications. Thus, an unmet medical need exists for a standalone SC or low frequency IV intervention to promote hemostasis and coagulation in patients with hemophilia in lieu of coagulation factor replacement therapy.

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

is 2.1- and 2.2-fold that of the general population, respectively, indicating a wide therapeutic index is associated with modulation of TFPI activity.[5] Additionally, single doses of PF-06741086 have been evaluated in a Phase 1 first-in-human study without significant adverse effects. These results suggest that TFPI may serve as an acceptable target for a pharmaceutical treatment to reduce inhibition of the extrinsic coagulation pathway and thereby increase clotting activity in patients with bleeding disorders, such as hemophilia.

1.2.1. 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 CCI [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, repeated dose administration of PF-06741086 and NovoSeven®RT (rFVIIa) was evaluated in rats in a 10-day IV investigative study. CCI [redacted]

[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.

1.2.2. Nonclinical Toxicology

The toxicity of intravenously or subcutaneously administered PF-06741086 was evaluated in nonpivotal CCI 8-day, repeat-dose studies in rats and monkeys and pivotal (GLP) studies in rats and monkeys CCI . 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, 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 and target organ toxicity; therefore the rat was suitable for use as the only species for evaluating chronic toxicity. Other toxicity studies included tissue cross reactivity assay, FcR and 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

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

The potential target organs identified in these studies was the coagulation cascade based on changes in D-dimer, PT, APTT and fibrinogen, with no clinical signs or microscopic evidence of bleeding or adverse thrombi/emboli formation. However, there were other effects on ALB, GLOB, ALB:GLOB and total protein values of rats and monkeys, the SC injection site of rats, and ADA's were observed in rats. Consistent with ICH S6 guidance, PF-06741086 was not evaluated in genotoxicity studies because it is not expected that this large molecule would interact directly with DNA or other chromosomal material.

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

1.3. Rationale

1.3.1. Clinical Experience with PF-06741086

1.3.1.1. Overall Safety

To date, a single clinical study has been completed with PF-06741086. The clinical development of PF-06741086 began in September 2015 with B7841001: a Phase 1, first-in-human (FIH) single ascending dose (SAD) study in healthy subjects. Male subjects between the ages of 18 and 55 with no known risk factors for thrombosis were eligible for this study. Subjects were enrolled sequentially into cohorts ordered by PF-06741086 maximum single-dose concentration and randomized to receive a single SC or IV dose of PF-06741086 or placebo. Data on safety, tolerability, PK, PD and immunogenicity were collected during clinic confinement (7 days) and outpatient follow-up (up to 84 days).

All doses of PF-06741086 were well-tolerated in study B7841001. There were no serious adverse events (SAEs). There were no severe treatment emergent adverse events (TEAEs). There were no reported infusion or injection site reactions following administration with PF-06741086.

Additional clinical information regarding PF-06741086 including data from study B7841001 may be found in the Investigators Brochure.

1.3.1.2. Plasma Pharmacokinetics of PF-06741086 Following Administration of Single IV and SC Doses of PF-06741086

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 3.

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 h following SC administration. Under the same dosing route, exposures (particularly AUC) appeared to increase greater than proportionally with dose, which suggests that PF-06741086 may undergo target-mediated drug disposition. As dose increases, mean terminal half-life of PF-06741086 increased from 33.3 h (100 mg SC) to 79.5 h (440 mg IV) in non-Japanese subjects.

Table 3. Descriptive Summary of Plasma PF-06741086 Pharmacokinetic Parameters Following Single SC and IV Doses, Study B7841001

	Parameter Summary Statistics by PF-06741086 Treatment Group					
Parameter (units)	30 mg SC	100 mg SC	300 mg SC	300 mg SC Japanese	150 mg IV	440 mg IV
N, n	4, 0	6, 4	6, 3	4, 2[b]	6, 6	6, 5
AUC_{inf} (ng.hr/mL)	NC	257700 (34)	2799000 (83)	4955000 (4240000-5670000)	2608000 (16)	14380000 (19)
AUC_{last} (ng.hr/mL)	0	81890 (391)	3120000 (68)	3551000 (28)	2346000 (14)	14290000 (21)
C_{max} (ng/mL)	0	1183 (287)	16490 (63)	18500 (25)	45640 (5)	152800 (12)
T_{max} (hr)	NR	48.0 (48.0-72.0)	72.0 (48.0-144)	108 (72.0-144)	1.07 (1.05-2.00)	1.54 (1.08-2.00)
$t_{½}$ (hr)	NC	33.30 ± 5.39	65.77 ± 18.00	98.35 (74.7-122)	43.58 ± 4.95	79.46 ± 17.71

N = Number of subjects contributing to the summary statistics; n = number of subjects for $t_{½}$ and AUC_{inf}.
NC=Not Calculated.
NR = Not reported: summary statistics are not presented for n<3.
[a] Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ±SD for $t_{½}$.
[b] Median and range presented since N=2.

1.3.1.3. Pharmacodynamics of PF-06741086 Following Administration of Single IV and SC Doses of PF-06741086

Pharmacologic effects reflective of coagulation pathway activation, which includes dPT, 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 PF-06741086 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 PF-06741086. 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 1-7 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.

1.3.2. Study Rationale

The clinical investigation of PF-06741086 will continue with study B7841002, an open-label, Phase 1b/2, multiple ascending dose (MAD) study in severe hemophilia A or B subjects, including subjects with inhibitors to factor VIII or factor IX. The clinical risk/benefit profile for this population is considered appropriate for the evaluation of safety, tolerability, PK, PD, and efficacy of multiple doses of PF-06741086. Frequency of bleeding episodes (of study subjects during treatment with PF-06741086) will be compared against the frequency of bleeding episodes in an external control group as a measure of therapeutic efficacy.

The primary objective of study B7841002 is to evaluate the safety and tolerability of multiple ascending doses of PF-06741086 administered by the SC or IV route. Secondary objectives include evaluating the PK and PD properties of PF-06741086, as well as assessing clinical efficacy based on the frequency of bleeding episodes. Selection of the PD endpoints and sampling schedule are based on results from non-clinical studies and the Phase 1 FIH study results. They will reflect either target binding by PF-06741086 (ie, TFPI level) 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 final 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.

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

1.3.3. Dose Rationale

1.3.3.1. Starting Dose

The starting dose for this study is 300 mg PF-06741086 SC once weekly (QW). The safety, PK, and PD results from study B7841001 (Section 1.3.1) were used to establish the starting dose in this study.

All dose levels (30-300 mg for SC, 150 and 440 mg for IV) evaluated in study B7841001 were safe and well-tolerated in healthy adult subjects; as such, the maximum tolerated dose (MTD) was not identified. In addition, as the primary target organ for pharmacologic effect of PF-06741086 in non-clinical toxicity studies was the coagulation cascade, the MTD in subjects with hemophilia would likely be higher than the MTD in healthy subjects with intact coagulation systems.

The efficacious dose of PF-06741086 was defined to have a trough concentration in the range of that conferring approximately 90% to 99% of maximum effect in the PD biomarker assay (EC_{90} to EC_{99}). This was selected as an approximately similar range indicated modulation of the in vivo biomarkers of PF1+2 and D-dimer reported with concizumab (a different anti-TFPI antibody) in healthy subjects and subjects with hemophilia.[6] Based on data from study B7841001, population PK/PD analyses of PD biomarker (ie, dPT, TGA peak thrombin, and PF1+2) data was conducted using nonlinear mixed-effects modeling with NONMEM (version 7.3). EC_{90} estimated from the peak thrombin, dPT and PF1+2 models

were 0.765, 2.84, and 35.4 µg/mL, respectively. While the EC_{90} of dPT is similar to that derived from a study in normal cynomolgus monkeys, ie, 2.25 µg/mL, the upper end of the wide range of EC_{90} derived from the three biomarkers (dPT, peak thrombin, and PF1+2) from B7841001 was also considered when the starting dose was selected to maximize the chance of achieving efficacy in hemophilia A and hemophilia B subjects. The predicted $C_{trough,ss}$ is 67.3 µg/mL following 300 mg weekly SC dosing of PF-06741086.

At the starting dose of 300 mg weekly SC in the current study, the steady state (SS) exposures (C_{max} and AUC_{168}) are predicted to be more than 150-fold lower than the PK stopping limits (Section 3.3). The predicted steady state (SS) exposures (C_{max} and AUC_{168}) at the starting dose are also lower than what were observed following single doses of 440 mg IV, the highest dose level evaluated in study B7841001.

1.3.3.2. Dose Progression

The dose progression in the study will be guided by observed safety, PK (including predicted exposures at subsequent dose levels), PD and/or efficacy. Regimens between the starting and highest doses will be selected with the intent to bracket the expected clinically efficacious exposure range in humans and to provide safety coverage for the expected clinically relevant dose range. PF-06741086 dose levels and/or regimen(s) may be modified after the first dose such that they can be administered at a higher or lower dose, by a different route (SC or IV), frequency (weekly or monthly), and with or without a loading dose, based on emerging data. However, they will not exceed the PK exposure or dose limitations for dose escalation (Section 3.3). The highest dose for SC dosing will also be determined by the total number of injections that can be safely administered in hemophilia patients.

Table 4 illustrates current predictions of the human PK based on data from Study B7841001 and the safety margins for the planned dose progression scheme. Nominal PF-06741086 doses planned are 300 mg SC QW, 150 mg SC QW (with a 300 mg SC loading dose), 450 mg SC QW, and 1000 mg IV QM.

Table 4. Estimated PK and Nonclinical Safety Margins for Planned PF-06741086 Doses

PF-06741086 Dose (mg)	Route (Frequency)	Estimated $C_{max,ss}$ [ng/mL] (fold NOAEL margin)	Estimated Ctrough,ss [ng/mL]	Estimated $AUC_{168,ss}$ [ng*hr/mL] (fold NOAEL margin)
300	SC (QW)	77000 CCI	66400	12300000 CCI
300 Loading	SC (single)	21000 CCI	15700	3220000 CCI
150	SC (QW)			
450	SC (QW)	134000 (208)	117000	21500000 CCI
1000	IV (QM)	313000 CCI	8980	26600000 CCI

Abbreviations: $AUC_{168,ss}$ = Area under the PF-06741086 concentration time curve from dosing to 168 hours after dosing at steady state; $C_{max,ss}$ = Maximum observed PF-06741086 concentration at steady-state; NOAEL = no observed adverse effect level in the most sensitive species; QM = once monthly; QW = once weekly

1.3.4. Summary of Risk/Benefit

Based on the potential risks, subjects will be monitored for treatment emergent events using the following parameters: serum chemistry, hematology, urinalysis, and coagulation assay laboratory values; vital signs; physical examinations; Electrocardiogram (ECG) parameters; and adverse events. Monitoring for antibody immune response will use a tiered testing strategy including measurement of ADA to PF-06741086 and further characterization of any positive antibody immune responses such as testing for neutralizing antibody. Additionally, subjects will be monitored for breakthrough bleeding events and any clinically-relevant effects that may impact hemostasis.

Safety was demonstrated at all tested single dose levels in the B7841001 FIH study. There did not appear to be any dose-related trends in the frequency of treatment emergent adverse events. Possible risks from treatment with PF-06741086 include the potential for thromboembolic and ischemic events, hypersensitivity reactions (including local injection/infusion site reactions), and antibody immune response with formation of anti-drug antibodies. However, it is expected that the potential risk of a thromboembolic or ischemic event in subjects with hemophilia will be lower than in healthy subjects due to the effects of FVIII or FIX deficiency.

The potential therapeutic efficacy of prophylaxis with PF-06741086 may be reflected in a reduced frequency of bleeding episodes versus the natural history of bleeding episodes for subjects using FVIII or FIX replacement therapy, or bypass agent therapy, for on demand treatment of bleeding episodes. Further, it is assumed that any occurrence of neutralizing antibodies against PF-06741086 will have no impact on prophylactic or episodic (on-demand) treatment with FVIII or FIX replacement or bypass agent therapy. These anticipated benefits may justify the potential risks of treatment with PF-06741086 for subjects with hemophilia A or B without inhibitors currently receiving factor replacement therapy, and subjects with inhibitors currently receiving bypass agent therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

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

2.1.1. Key Secondary Objective

- To assess the clinical efficacy of repeat dosing of PF-06741086.

2.1.2. Secondary Objectives

- To characterize the PK profile of PF-06741086.
- To characterize the PD profile of PF-06741086.
- To characterize the immunogenicity of PF-06741086.

CCI [redacted]

2.2. Endpoints

2.2.1. Primary Endpoints - Safety

- Frequency, severity and causal relationship of treatment emergent adverse events (AEs) (treatment emergent adverse events [TEAEs]) and withdrawals due to TEAEs; Day 1 up to Day 113.

- 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 113.

- 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 113.

- Frequency, severity and causal relationship of infusion and injection site reactions; Day 1 up to Day 113.

2.2.2. Secondary Endpoints

- Efficacy:
  - Frequency and annualized rate of bleeding episodes; Day 1 up to Day 85.
- Pharmacokinetics:
  - Plasma PF-06741086 concentrations (Day 1 up to Day 113) and noncompartmental parameters will be calculated as determined by a validated assay:
    - Single-dose.
    - Day 1 to Day 7 (QW): C_{max}, T_{max}, AUC_{last}, C_{168h}.
    - Day 1 to Day 28 (QM): C_{max}, T_{max}, AUC_{last}, C_{672h}.
    - Multiple-dose Day 29 to Day 36 (QW) or Day 29 to Day 57 (QM) $C_{max,ss}$, $T_{max,ss}$, AUC_{τ}, V_{ss} (for IV administration only), CL (for IV administration only) or CL/F (for SC administration only), and C_{min}.
- Pharmacodynamics:
  - Total TFPI; Day 1 up to Day 113.

- Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); Day 1 up to Day 113.
- Prothrombin fragment 1+2; Day 1 up to Day 113.
- D-dimer; Day 1 up to Day 113.
- Dilute prothrombin time; Day 1 up to Day 113.

- Immunogenicity:
  - Frequency of anti-drug antibody (ADA) and neutralizing antibody (NAb) production against PF-06741086; Day 1 up to Day 113. Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay.

CCI [redacted]

[redacted]

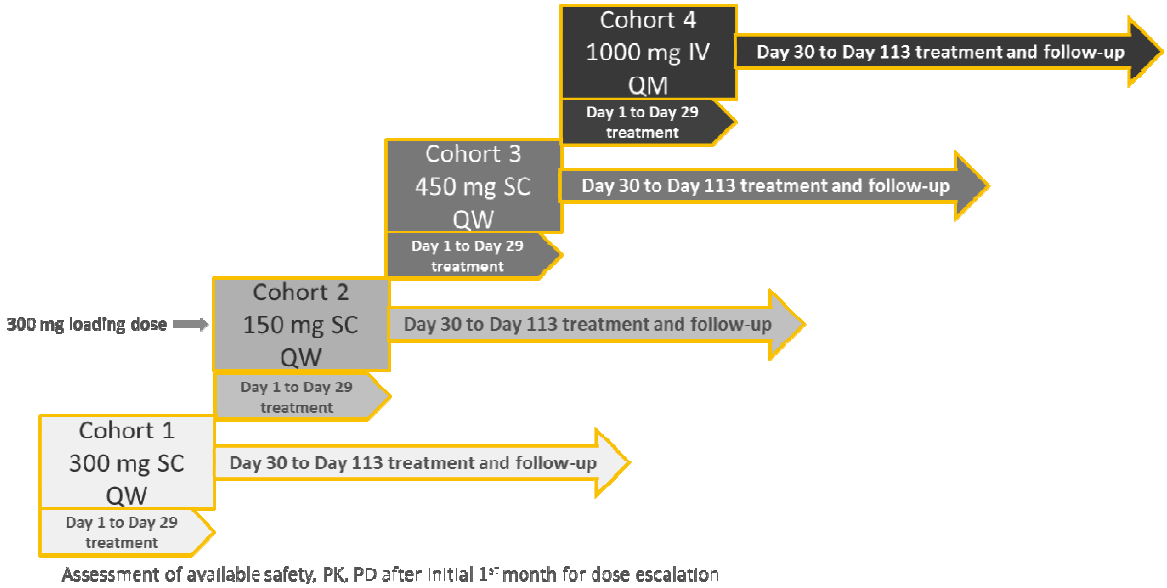
3. STUDY DESIGN

B7841002 will be an open-label investigation of the safety, tolerability, PK, PD, and efficacy of multiple SC or IV doses of PF-06741086 in males with hemophilia A or B, with or without inhibitors to FVIII or FIX. The subjects, investigator, site personnel, and Sponsor will not be blinded to the treatment assignment.

Subjects with severe hemophilia A or B (defined by factor VIII or factor IX activity ≤1%), including subjects with inhibitors to factor VIII or factor IX (positive inhibitor test result [above the upper limit of normal]), who receive bypass agents as primary treatment for bleeding episodes) will be recruited into B7841002. Subjects with inhibitors who are currently treated with activated prothrombin complex concentrate (APCC, eg, FEIBA) and cannot substitute treatment with recombinant factor VIIa (rFVIIa, eptacog alfa [activated]) as their standard of care for treatment of acute bleeding episodes (at a dose level of approximately 90 µg/kg) for the duration of the study are not eligible. Subjects must be on an episodic (on-demand) treatment regimen at the time of study enrollment and also have a documented history of at least 6 acute bleeding episodes in the 6 months prior to study enrollment. Subjects must washout from any factor replacement or *bypass* agent therapy prior to screening and prior to study treatment.

The following schematic is meant to demonstrate the planned dose progression scenario:

Figure 1. Dose Progression Scheme



SC or IV multiple dose cohorts will be enrolled starting at the 300 mg SC dose. Subjects will be enrolled and assigned to treatment as follows.

- Cohort 1 (n=6): 300 mg PF-06741086 SC QW (n=6).
- Cohort 2 (n=6): 300 mg SC loading dose, 150 mg PF-06741086 SC QW (n=6).
- Cohort 3 (n=6): 450 mg PF-06741086 SC QW (n=6).
- Cohort 4 (n=6): 1000 mg PF-06741086 IV QM (n=6).

Doses, frequency and route(s) of administration after the first dose may be modified based on review of available data. Additional subjects or cohorts may be added for reasons described in Section 3.1.

Safety endpoints will include TEAEs (graded by the NIAID DMID severity scale), infusion/injection site reactions, laboratory parameters that may be modulated due to coagulopathy (eg, PT/INR, activated aPTT, fibrinogen, ATIII, platelet counts) and parameters to screen for possible thrombotic events (eg, cardiac troponin I). PK and PD endpoints include concentrations of PF-06741086 in plasma, non-compartmental PK parameters, measures of target binding by PF-06741086 (ie, TFPI level) or downstream pharmacological activities of TFPI inhibition (ie, dPT, thrombin generation, PF1+2, and D-dimer).

3.1. Planned Number of Subjects

Approximately 24 subjects are planned for enrollment at approximately 20 study sites. Subjects who are withdrawn for reasons other than safety may be replaced at the discretion of the Sponsor. Subjects with inhibitors to FVIII or FIX will only be enrolled into a cohort with a dose level and regimen that was previously assessed as safe and well tolerated in subjects without inhibitors. Additional subjects and/or cohorts may be enrolled in the event that the number of dosing cohorts or size of dosing cohorts is increased to fully define the dose range and/or clinical profile at the respective dose levels.

3.2. Study Duration

Subjects will be screened within 35 days prior to administration of the investigational product to confirm that they meet the subject eligibility criteria for the study. At the Day 1 clinic visit, eligibility criteria will be confirmed. Subjects will begin dosing on Day 1. Subjects will be required to return to the clinic (eg, study site) for PK/PD sample collection on Day 2 and Day 4. Subjects will then be required to attend weekly clinic visits on Day 8, Day 15, Day 22, and Day 29. For subjects with once weekly (QW) dosing frequency, investigational product will be administered at these visits as well.

Following Day 29, provided that safety was confirmed for the cohort and no stopping criteria were met, all subjects in each cohort will return to the clinic for PK/PD sample collection on Day 30 and Day 33. Subjects in the SC cohorts will receive treatment on Day 36, Day 43, Day 50, Day 57, Day 64, Day 71, Day 78, follow-up on Day 85, and end-of-study procedures on Day 113. For the Day 36, 43, 50, 64, 71 and 78 SC treatments, in countries where approved by respective competent authorities and at sites where it is approved by the respective IRB/EC, SC treatment with investigational product may be administered by investigator site personnel in a home care or ambulatory clinic setting. Subjects in the IV cohort will receive treatment on Day 57, follow-up on Day 85, and end-of-study procedures on Day 113.

Subjects with positive ADA or NAb results may be requested to return for additional follow-up visits after Day 113.

Subjects who experience a treatment-related adverse event (including lab abnormalities) 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 subject, from initial screening to final follow-up, will be approximately 5 months.

During the study data will be reviewed on an ongoing basis to determine if PF-06741086 is safe and tolerated. Dosing of subjects in any cohort may be stopped if the B7841002 protocol-specified stopping criteria are met (Section 3.3). If available data are permissive for dose progression, subjects will be recruited into the next cohort in the study and dosed at the next dose level of PF-06741086.

3.3. Dose Escalation and Stopping Rules

Dose escalation stopping rules will be used to determine whether the maximum tolerated dose has been attained.

Dose escalation will not occur if 2 or more dose-limiting toxicities are met within a dosing cohort of 6 subjects. Dose escalation may occur if ≤1 dose limiting toxicity is observed within a dosing cohort of 6 subjects. Dose limiting toxicities are defined as:

- Treatment emergent laboratory abnormality as specified in Appendix 2;
- Treatment emergent vital sign abnormality as specified in Appendix 2;
- Treatment emergent ECG abnormality as specified in Appendix 2;
- Treatment emergent severe or ≥ Grade 3 adverse event, as graded by the NIAID DMID criteria for severity unless incontrovertibly due to extraneous causes.

Additional rules governing dose escalation are as follows:

- Dosing at the current dose level (or higher dose levels) will be suspended for any treatment emergent thrombotic event (see Appendix 1 for qualifying AEs) in a subject receiving PF-06741086 to permit characterization of the respective event and communication to regulatory agencies where required. Vessel occlusion related to the insertion or presence of a central venous catheter may be excluded from this criterion after review of the AE with the respective investigator to assess causality and/or clinical significance.
- All treatment emergent adverse events, regardless of system organ class, severity/grade, causality, and/or attribution to treatment with PF-06741086 are assessed and it is determined by the Sponsor that the limit of safety and/or tolerability has been reached.
- Dose escalation will be paused for any treatment emergent serious adverse event (SAE) that occurs in a subject receiving PF-06741086 until causality is fully assessed by the Sponsor. Dose escalation will cease if the SAE is determined to be either drug-related or unknown, and may resume if the SAE is determined to be not drug-related by the Sponsor.
- If, based on the observed data, the group geometric mean C_{max} or area under the curve (AUC_{168}) (based on total concentration with either the first dose or at steady-state) of the next planned regimen is projected to exceed the exposure limits (AUC_{168} of 1,940,000 μg•h/mL and C_{max} of 27,800 μg/mL), that dose will not be explored. Modified doses may be explored if they are not expected to exceed these PK stopping criteria.

In addition, tolerability criteria for dose escalation are:

- For SC cohorts: no more than 2 subjects in a dosing cohort of 6 subjects experience at least moderate severity injection site reactions.

- For IV cohorts: no more than 2 subjects in a dosing cohort of 6 subjects experience at least moderate severity infusion/injection site reactions.

Progression to a higher dose level or regimen not assessed as safe and well tolerated in a previous cohort will follow the Sponsor's review of the available safety, PK, PD, and bleed rate data through study Day 29 (at a minimum) in 100% (ie, 6 of 6) of subjects in the current cohort. Accumulated safety, PK, PD, bleed rate and immunogenicity data from previous cohorts will also be reviewed. Progression to the next cohort will occur if the current dose level is well tolerated and after satisfactory review of these data.

For doses with projected C_{max}/AUC levels not previously achieved in humans, sequential dosing will be implemented for the first 3 subjects at the respective dose level. Following initial dosing for each of the first 3 subjects, available safety and laboratory data through 72 hours post-dose will be monitored. Subsequent dosing for the cohort shall not commence until satisfactory review of these data is complete.

If at any time during cohort enrollment data suggest that stopping rules may have been met then dosing will be suspended. A formal review of available data by the Sponsor study team will determine whether stopping rule criteria have been met.

Dose Modifications

Any subject who experiences a dose limiting toxicity (per Appendix 2) will be discontinued from treatment with the investigational product and will be followed for adverse event monitoring until resolution of the respective toxicity and elimination of study drug or the end of the study (Day 113) and resolution or stabilization of the respective toxicity, whichever occurs first. In addition, subjects who have not experienced dose limiting toxicities but are currently receiving a dose that met the dose limiting toxicities criteria for termination of dose escalation as defined in Section 3.3 will be removed from the current dose level and dropped to the next lowest exposure level.

Subjects who have not experienced a dose-limiting toxicity may also require dose modifications. Criteria for modifications of dosing in an individual subject are as follows:

- Moderate severity infusion/injection site reactions at more than 2 consecutive visits (eg, Day 22, Day 29, and Day 36);

- Treatment emergent adverse event(s) that increases in severity/grade, without resolution, (eg, Mild to Moderate and continuing) after repeat administration of PF-06741086;

- Treatment emergent adverse event(s) of any severity with more than 2 occurrences following repeat administration of PF-06741086.

Any subject who meets the above criteria during treatment with PF-06741086 will be removed from the current dose level and dropped to the next lowest exposure level, unless the event(s) are incontrovertibly due to extraneous causes or are incontrovertibly complications of hemophilia (see Section 8.6 for qualifying events).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects 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 subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment in the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) has been informed of all pertinent aspects of the study.

2. Males ≥18 and <65 years of age.

3. Body Mass Index (BMI) ≥17.5 and ≤30.5 kg/m^2 and total body weight ≥50 and ≤100 kg.

4. Diagnosis of severe hemophilia A or B (Factor VIII or Factor IX activity ≤1%).

5. Subjects enrolled as Factor VIII or Factor IX inhibitor patients must have a positive inhibitor test result (above the upper limit of normal) at the local laboratory and must receive a bypass agent as primary treatment for bleeding episodes. A positive inhibitor test result will be above the upper limit of normal for the assay. Inhibitor test results from up to 6 months prior to Day 1 may be used to meet this requirement.

6. Patients with an episodic (on-demand) treatment regimen prior to Screening, who are willing and able to washout from Factor VIII (for at least 72 hours) or Factor IX (for at least 96 hours) replacement therapy, or bypass agent therapy (for rFVIIa and APCC: at least 72 hours), prior to Screening laboratory assessments of factor activity and have no plans to institute prophylactic factor treatment during the study period.

7. Had at least 6 acute bleeding episodes (spontaneous/traumatic) during the 6-month period prior to Screening. Surgical bleeding episodes do not apply to this criterion.

8. If receiving therapy for human immunodeficiency virus (HIV) or active hepatitis infection, have stable disease and be on a stable regimen at the time of study entry (ie, stable dosing for at least 3 months before consent).

9. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

10. If with partners currently pregnant or if able to father children, agree to use a highly effective method of contraception throughout the study and for least 28 days after the last dose of investigational product.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Females.

2. Known coronary artery, thrombotic, or ischemic disease.

3. Known hemostatic defect other than hemophilia A or B.

4. ATIII, Protein C, or Protein S deficiency, Factor V Leiden, Prothrombin 20210 mutation, or other known pro-thrombotic condition

5. Currently receiving treatment for acute bleeding episodes with APCC (eg, Factor Eight Inhibitor Bypass Agent [FEIBA]) and cannot substitute treatment with rFVIIa at a dose level of approximately 90 μg/kg for the duration of the study.

6. Regular, concomitant therapy with immunomodulating drugs (eg, intravenous immunoglobulin [IVIG], and routine systemic corticosteroids).

7. Abnormal renal or hepatic function as defined by the following laboratory results at Screening:

    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels >3 times the upper limit of normal (ULN).

    - Total bilirubin level >2 mg/dL (>35 μmol/L).

    - Serum albumin < the lower limit of normal (LLN).

    - Serum creatinine level >1.25 times the ULN.

8. Abnormal hematology values as defined by the following laboratory results at Screening:

    - Platelet count <100,000/μL.
    - Fibrinogen level < LLN.
    - Hemoglobin level <10 gm/dL.

9. Abnormal coagulation activity as defined by the following laboratory results at Screening:

    - Prothrombin time (PT) >1.25 times the ULN.

10. CD4 cell count ≤200/μL.
11. Known hypersensitivity or allergic reaction to hamster protein.
12. Known sensitivity to heparin or heparin-induced thrombocytopenia.
13. Investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
14. Participation in other studies involving investigational drug(s) within 30 days (or as determined by the local requirement, whichever is longer) or 5 half-lives prior to study entry and/or during study participation.
15. Other severe acute or chronic medical or psychiatric condition 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 subject inappropriate for entry into this study.
16. With partners currently pregnant or able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
17. Had major surgery, as judged by the investigator, within 3 months prior to the study or have elective surgery planned during the study.

4.3. Randomization Criteria

This study is not a randomized trial, but allocation to treatment will follow procedures similar to randomization (which may be referred to as enrollment).

All subjects will be given PF-06741086. Subjects will be assigned a randomization number provided they have satisfied all eligibility criteria and the following enrollment criteria:

1. Subjects must washout from Factor VIII (for at least 72 hours) or Factor IX (for at least 96 hours) replacement therapy and from treatment with any other intravenous hemostatic agent (for at least 72 hours) prior to the Day 1 visit laboratory testing for clotting factor activity level. Subjects cannot be enrolled or treated with investigational product if they have received treatment for an acute bleeding episode with Factor VIII or Factor IX replacement therapy within 72 hours or 96 hours, respectively, or rFVIIa or APCC (eg: FEIBA) bypass agent therapy within 72 hours, of the Day 1 visit. If factor replacement or bypass agent therapy is required to treat a bleeding episode during the Screening period, then the subject may return for the Day 1 visit after completing the required washout period and remain eligible for study participation. See Section 6.1 for further Screening procedure guidance.

4.4. Lifestyle Guidelines

All male subjects who are able to father children and, in the opinion of the investigator, are sexually active and at risk for pregnancy with their partners must agree to use a highly effective method of contraception consistently and correctly for the duration of the study and for at least 28 days after the last dose of investigational product. A longer duration of contraception usage may be required if data from B7841002 warrant this change. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (ie, oral, inserted, injected, implanted, transdermal) provided the subject's partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed intrauterine device (IUD) or intrauterine system (IUS).

3. Male condom WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Female partner who meets the criteria for non-childbearing potential, as described below:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female partners (including females with tubal ligations) will be considered to be of childbearing potential.

   All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing through discharge from the study.

4.5. 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, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational 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 investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational 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 subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

Study Treatment	Route of Administration	Protocol Term
PF-06741086, Solution for Injection, 100 mg/mL [redacted]	subcutaneous (SC)	investigational product (IP)
PF-06741086, Solution for Injection, 100 mg/mL [redacted]	intravenous (IV)	investigational product (IP)

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Allocation of subjects to treatment groups will proceed through the use of an interactive response technology (IRT) system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number and the date of birth of the subject. The site personnel will then be provided with a treatment assignment and dispensable unit (DU) or container number when drug is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24-hour-a-day, 365-days-a-year IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

5.2. Subject Compliance

Subjects assigned to SC cohorts will receive weekly treatment administration Day 1 to Day 78 (see Section 3.2). Subjects assigned to the IV cohort will receive monthly treatment administration from Day 1 to Day 57.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

PF-06741086 Solution for Injection, 100 mg/mL [redacted], will be supplied by Pfizer as a good manufacturing practice (GMP) manufactured, sterile liquid solution for injection packaged in a 6 mL glass vial sealed with a stopper and an aluminum seal (nominal fill volume of 1.0 mL).

These products will be supplied to sites as open label packaged supplies for subsequent unit dosing.

5.3.2. Preparation and Dispensing

See the Investigational Product Manual (IPM) 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, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Each vial is for single-use only. Vials are for use in a single patient for a single dose.

5.4. Administration

Investigator site personnel will administer investigational product according to the Investigational Product Manual (IPM). When dosing is by IV infusion, the IV infusion will be on the opposite arm from PK sampling.

For subjects receiving SC injection(s), the number of injections and injection sites will be recorded. The preferred body locations of the SC injection(s) are the front of the middle of the 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. Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection doses). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided.

5.5. Investigational Product Storage

See the IPM for complete information on storage, handling and stability of investigational drug product.

The investigator or an approved representative (eg, pharmacist) will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the IPM for storage conditions of the product.

Storage conditions stated in the single reference safety document (SRSD) (eg, investigator's brochure [IB]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for

excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the Sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s)

- Subjects will abstain from all prohibited concomitant medications, except for the treatment of adverse events or acute bleeding episodes as described in Section 5.7.1 of this protocol.

- All concomitant treatments taken during the study must be recorded with indication, and start and stop dates of administration. All subjects will be questioned about concomitant treatments at each clinic visit.

- 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 subject 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.

5.7.1. Prohibited Medications

Factor VIII (within 72 hours) or Factor IX replacement therapy (within 96 hours), or bypass agent therapy (FVIIa 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 subject experiences an acute bleeding episode during this washout period requiring treatment with a Factor VIII or IX replacement therapy, or bypass agent therapy, the subject 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), or bypass agent therapy (for FVIIa or APCC: at least 72 hours), before Day 1 treatment is also prohibited. If a subject experiences an acute bleeding episode during this washout period requiring treatment with a Factor VIII or IX replacement therapy, or bypass agent therapy, the subject 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 is prohibited throughout the study.** If a subject receiving investigational product is subsequently administered a rFVIIa dose greater than approximately 90 µg/kg, the investigator must immediately contact the Sponsor's medical monitor to discuss the case to determine if the respective subject should continue to receive IP, remain in the study, or be withdrawn immediately.

Treatment with APCC (eg, FEIBA) is prohibited throughout the study. Subjects receiving such therapy, who cannot substitute treatment with rFVIIa, at the 90 µg/kg per dose are not to be enrolled into this study. Subjects who are treated with investigational product who are subsequently administered APCC therapy must be withdrawn from treatment with investigational product immediately. These subjects should be followed at all remaining clinic visits up to Day 113 to monitor for adverse events and any additional safety concerns.

The use of immunomodulatory medications (eg, Intravenous Immunoglobulin (IVIG), routine systemic corticosteroids) is prohibited during the study.

The use of antifibrinolytic agents or medications known to influence platelet function (eg, aspirin or certain non-steroidal anti-inflammatory drugs) within 5 days before initial study drug administration through Day 113 is prohibited.

5.7.2. Treatment(s) for Acute Bleeding Episodes

If a subject experiences an acute bleeding episode at any point throughout the study, the subject is to be stabilized utilizing the subject's standard hemostatic treatment regimen

(which may include Factor VIII or Factor IX replacement therapy, or rFVIIa bypass agent therapy at approximately 90 µg/kg per dose). Pausing or withdrawal of treatment with investigational product is not required in the event of a breakthrough bleed, but may be considered at the discretion of the investigator. See Section 7.2.5 for additional information.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 35 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section.

All screening procedures must be repeated for any subject who failed initial screening procedures and is re-screening into the study, with the exception of the following labs related to genetic mutation screening or pharmacogenomics samples:

- Prothrombin 20210 mutation testing;
- Factor V Leiden mutation testing;
- Banked biospecimens;
- Factor VIII and Factor IX activity;
- Factor VIII or Factor IX inhibitor (this test is only required for subjects with a hemophilia history of inhibitors).

The following procedures will be completed during Screening:

- Obtain written informed consent;
- Review Inclusion and Exclusion criteria;
- Obtain medical history, including hemophilia history and inhibitor history, and collect the number of bleeding episodes over the past 6 months;
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken since the start of Screening;
- Review use of Factor VIII or Factor IX replacement therapy, or bypass agent therapy, to ensure subject meets washout criteria prior to Screening;
- Collect demography and height;
- Collect weight;

- Provide instructions regarding study contraception requirements;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Conduct full physical examination (PE). On and after Day 1 and at the discretion of the investigator, limited physical examinations based on signs and symptoms will be performed, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Collect single 12-lead ECG. If ECG is abnormal, collect triplicate ECG.
- Collect blood specimens for the following for analysis at a local laboratory, if necessary:
    - Factor VIII or Factor IX inhibitor (this test is only required for subjects with a hemophilia history of inhibitors). Inhibitor test results from up to 6 months prior to Day 1 may be used to meet this requirement.
- Following at least a 4-hour fast (and at least a 12-hour fast prior to lipid panel), collect blood and urine specimens for the following for shipment to the study central laboratory:
    - Urinalysis;
    - Serum chemistry;
    - Hematology;
    - Factor VIII and Factor IX activity;
    - CD4 cell count;
    - Prothrombin 20210 mutation testing;
    - Factor V Leiden mutation testing;
    - Lipid panel;
    - Protein C activity/Protein S level;
    - Serology (HBs Ag, HBc Ab, HCV Ab, and HIV);
    - PT/INR;
    - aPTT;
    - Fibrinogen;

- ATIII.

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital signs and prior to blood specimen collection;
- Blood pressure/pulse rate: prior to blood specimen collection;
- Pharmacokinetic blood specimens: samples collected in sodium citrate tubes should not be the initial tube of blood collected;
- Other procedures.

When an IV catheter is utilized for blood sample collections, ECGs and vital signs (pulse rate, respiratory rate, blood pressure and oral temperature) assessments should be collected prior to the insertion of the catheter.

6.2.1. Day 1 Visit

Prior to dosing on Day 1 the following procedures will be completed:

- Assess baseline symptoms/AEs including interval since Screening;
- Review changes in subject's concomitant treatment information since Screening;
- Review use of Factor VIII or Factor IX replacement therapy, or rFVIIa bypass agent therapy to ensure subject meets washout criteria prior to Day 1;
- Review changes in the subject's medical history including medication history since Screening;
- Collect information on new bleeding episodes;
- Review Inclusion and Exclusion criteria;
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes since Screening of any ongoing symptoms;
- Collect weight;
- Confirm proper contraception is being used;

- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect triplicate 12-lead ECG.
- Collect blood and urine specimens for the following for shipment to the study central laboratory:
  - Urinalysis;
  - Serum chemistry;
  - Hematology with differential panel;
  - Factor VIII and Factor IX activity;
  - Banked biospecimens;
  - TFPI level;
  - PT/INR;
  - aPTT;
  - Fibrinogen;
  - ATIII;
  - TGA;
  - PF1+2;
  - D-dimer;
  - dPT;
  - Cardiac Troponin I;
  - PK blood sampling;
  - Immunogenicity (ADA, NAb);
  - [redacted]
- Treatment assignment any time prior to dosing once subject has met all eligibility criteria;

- After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- **IV cohorts only**: Collect blood samples from the arm not used for IV IP administration immediately following completion of the IV line flush after completion of the IV infusion. These blood samples are for shipment to the study central laboratory:
  - TFPI level;
  - TGA;
  - PF1+2;
  - D-dimer;
  - dPT;
  - PK blood sampling.
- Monitor infusion/injection site reactions.
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Issue subject diary and provide training with respect to completing the diary including timing and nature of information to be entered.

6.2.2. Day 2 (-6 hours/+1 day) and Day 4 (-6 hours/+1 day) PK/PD Blood Draws

The following procedures will be completed 24 (-6/+24) and 72 (-6/+24) hours following investigational product administration on Day 1:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect blood samples for the following for shipment to the study central laboratory:

- TFPI level;
- TGA;
- PF1+2;
- D-dimer;
- dPT;
- PK blood sampling.

6.2.3. Day 8 (±1 day), Day 15 (±2 days), Day 22 (±2 days) and Day 29 (±2 days) Visits

The following procedures will be completed:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Collect weight (**Day 29 only**);
- Confirm proper contraception is being used;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary;
- Collect single 12-lead ECG. If ECG is abnormal, collect triplicate ECG;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect urine for urinalysis for shipment to the study central laboratory.
- Collect blood samples for the following for shipment to the study central laboratory:
  - Serum chemistry;
  - Hematology (with differential panel on Day 29 only);
  - TFPI level;

- PT/INR;
- aPTT;
- Fibrinogen;
- ATIII;
- TGA;
- PF1+2;
- D-dimer;
- dPT;
- Cardiac Troponin I;
- PK blood sampling;
- Immunogenicity (ADA, NAb) **(Days 15 and 29 only)**;
- [redacted]

- **Cohorts with SC administration**: After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections) (**Days 8, 15, 22 and 29**).

- **Cohorts with IV administration**: After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections) (**Day 29 only**)

After dosing, the following procedures will be completed:

- **IV cohorts only** (**Day 29 only**): Collect blood samples from the arm not used for IV IP administration immediately following completion of the IV line flush after completion of the IV infusion. These blood samples are for shipment to the study central laboratory;

- Monitor infusion/injection site reactions;

- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.4. Day 30 (-6 hours/+1 day) and Day 33 (-6 hours/+1 day) PK/PD Blood Draws at Clinic Visits

The following procedures will be completed 24 (-6/+24) and 96 (-6/+24) hours following investigational product administration on Day 29:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Collect blood samples for the following for shipment to the study central laboratory:
  - TFPI level;
  - TGA;
  - PF1+2;
  - D-dimer;
  - dPT;
  - PK blood sampling.

6.2.5. Day 36 (±2 days), Day 43 (±2 days) and Day 50 (±2 days) Visits

The following procedures will be completed:

- **Cohorts with SC administration**: administer the investigational product (see STUDY TREATMENTS and Administration Sections);
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary;
- Report information regarding the use of concomitant treatment and the occurrence of adverse events.

6.2.6. Day 57 (±2 days) Visit

The following procedures will be completed:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Confirm proper contraception is being used;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary;
- Collect weight;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect urine for urinalysis for shipment to the study central laboratory.
- Collect blood samples for the following for shipment to the study central laboratory:
    - Serum chemistry;
    - Hematology;
    - TFPI level;
    - PT/INR;
    - aPTT;
    - Fibrinogen;
    - TGA;
    - PF1+2;
    - D-dimer;
    - dPT;

- PK blood sampling;
- Immunogenicity (ADA, NAb);
- [redacted]
- After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections).

After dosing, the following procedures will be completed:

- **IV cohorts only**: Collect blood samples from the arm not used for IV IP administration immediately following completion of the IV line flush after completion of the IV infusion. These blood samples are for shipment to the study central laboratory;
- Monitor infusion/injection site reactions;
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.2.7. Day 64 (±2 days), Day 71 (±2 days) and Day 78 (±2 days) Visits

The following procedures will be completed:

- **Cohorts with SC administration**: administer the investigational product (see STUDY TREATMENTS and Administration Sections);
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary;
- Report information regarding the use of concomitant treatment and the occurrence of adverse events.

6.2.8. Day 85 (±2 days) Visit

The following procedures will be completed:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Monitor infusion/injection site reactions;

- Collect information on new bleeding episodes;
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Confirm proper contraception is being used;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary;
- Collect weight;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect urine for urinalysis for shipment to the study central laboratory.
- Collect blood samples for the following for shipment to the study central laboratory:
  - Serum chemistry;
  - Hematology with differential panel;
  - TFPI level;
  - PT/INR;
  - aPTT;
  - Fibrinogen;
  - TGA;
  - PF1+2;
  - D-dimer;
  - dPT;
  - PK blood sampling;
  - Immunogenicity (ADA, NAb);
  - [redacted]

6.3. Follow-up Visit/End of Study

6.3.1. Day 113 (±7 days) Visit

The following procedures will be completed:

- Obtain information regarding the use of concomitant treatment and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Provide instructions regarding study contraception requirements;
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions;
- Collect weight;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect urine for urinalysis for shipment to the study central laboratory.
- Collect blood samples for the following for shipment to the study central laboratory:
    - Serum chemistry;
    - Hematology with differential panel;
    - TFPI level;
    - PT/INR;
    - aPTT;
    - Fibrinogen;
    - TGA;

- PF1+2;
- D-dimer;
- dPT;
- PK blood sampling;
- Immunogenicity (ADA, NAb);
- Subjects with positive ADA or NAb may be required to attend additional, unscheduled follow-up visits after Day 113. Extended follow-up visits every 2 weeks for up to 3 months, including vital signs, immunogenicity, AE and concomitant treatment assessments, may be performed.

- Discharge from study.

6.4. Subject Withdrawal

Withdrawal of consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or persons previously authorized by the subject to provide this information. Subjects 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 post treatment study follow-up, and entered on the appropriate case report form (CRF) page. Publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), if applicable, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events.

If a subject withdraws prior to Day 113, the following assessments should be completed:

- Obtain information regarding the use of concomitant medication and the occurrence of adverse events;
- Collect information on new bleeding episodes;
- Monitor infusion/injection site reactions;
- Assess symptoms by spontaneous reporting of adverse events and by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes from baseline/previous visits of any ongoing symptoms;
- Confirm proper contraception is being used;
- Collect the subject's diary and review with the subject/caregiver, if applicable, including information about study compliance, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions;
- Collect weight;
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure;
- Collect urine for urinalysis for shipment to the study central laboratory.
- Collect blood samples for the following for shipment to the study central laboratory:
    - Serum chemistry;
    - Hematology;

- TFPI level;
- PT/INR;
- aPTT;
- Fibrinogen;
- TGA;
- PF1+2;
- D-dimer;
- dPT;
- PK blood sampling;
- Immunogenicity (ADA, NAb);
- Subjects with positive ADA or NAb may be required to attend additional, unscheduled follow-up visits. Extended follow-up visits every 2 weeks for up to 3 months, including vital signs, immunogenicity, AE and concomitant medication assessments, may be performed.

- Subjects who are ADA or NAb positive, who have also been administered FVIIa or FEIBA, should be followed at all remaining clinic visits up to Day 113 or up to 3 months following positive ADA/NAb results, whichever is longer.

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

7. ASSESSMENTS

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

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES 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 labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count 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	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	Factor V Leiden mutation[b] Prothrombin 20210 Mutation[b] HBs Ag[b] Total HbcAb[b] HCVAb[b] HIV[b] Anti-thrombin III Protein C activity[b] Protein S level[b] PT/INR aPTT Fibrinogen Cardiac Troponin I Factor VIII[c] Factor IX[c] Factor VIII and Factor IX inhibitor [d] Lipid profile[b] CD4 cell count[b]
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat) Total bilirubin (repeat) Albumin (repeat) Alkaline phosphatase (repeat) Direct bilirubin Indirect bilirubin Creatine kinase GGT PT/INR		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only.
c. At Screening and Day 1 only.
d. Only At Screening and only for subjects with hemophilia history of inhibitors, if necessary. Inhibitor test results from up to 6 months prior to Day 1 may be used to meet requirement.

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. Upon completion of the study, retained safety samples may be used for the assessment of CCI samples to be used for this purpose will be packaged and shipped to Pfizer's BioBank for storage. These data will not be included in the clinical study report. Samples will be retained in Pfizer's Biobank for up to 1 year following completion of the study.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects 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.

7.1.3. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times specified in the Schedule of Activities. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) should be used throughout the study. Blood pressure should not be taken from the arm with an IV infusion. Subjects should be instructed not to speak during measurements.

Where possible, the same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring blood pressure (BP) and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.4. Respiratory Rate

Respiratory rate should be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject 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.

7.1.5. Temperature

Temperature will be measured orally. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.1.6. Electrocardiogram

ECGs should be collected at times specified in the Schedule of Activities.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs (**Day 1 only**) will be obtained approximately 2-4 minutes apart; the average of the triplicate ECG measurements collected at each nominal time point on Day 1 will serve as each subject's baseline QTcF value.
To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurements. If the QTcF interval is increased by ≥45 msec from the baseline, or an absolute QTcF value is ≥500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the average of QTcF values from the triplicate measurements remains above the threshold value (≥45 msec from the baseline; or is ≥500 msec), then a single ECG must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTcF values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTcF intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

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. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTcF values are in the acceptable range.

7.1.7. Injection and Infusion Site Reactions

Injection site reactions will be assessed according to the Schedule of Activities. Injection site reactions may include but are not limited to: erythema, induration, ecchymosis, pain and pruritus. The size and severity of injection site reactions will be assessed and documented. If deemed appropriate by the investigator, a consultation with a dermatologist will be performed. Documentation may include a dermatologist report, clinic notes and photographs.

7.2. Efficacy

7.2.1. Hemophilic Bleeding Episodes

During this study, the investigator (or qualified designee) will review the subject diary with the subject, and inquire about and record AEs, concomitant treatments, bleeding episodes (including location and etiology – traumatic or spontaneous) and any hemostatic treatments (including intravenous treatments with factor VII products, factor IX products or bypass agents). Hemostatic therapy that is administered to treat bleeding episodes during the Screening period and during the study through the final study visit will be documented as concomitant treatment. Subject diary review will include any bleeding episodes treated with hemostatic agents. Bleeding episodes requiring treatment with intravenous coagulation factor products or bypass agents will count toward the determination of bleeding episode frequency during the period of treatment with PF-06741086. Subject assessment(s) will be captured on the subject diary and reviewed by the investigator at study visits. One assessment per infusion will be required.

7.2.2. Bleeding

Occurrences of bleeding episodes treated with hemostatic agent(s) will be obtained from subject diaries and medical records. Where relevant, investigators (or designee) and monitors will ensure that there is consistency between the subject's medical record and/or subject diaries and the CRFs. Bleeding episodes will not be reported as AEs unless associated with a serious adverse event, although the concomitant events associated with a bleed may be reported as an AE if appropriate (eg, a fracture, pain – see Section 8.6 below for guidance on hemophilia related events). Both spontaneous bleeding episodes and traumatic bleeding episodes will be collected. Only bleeding episodes that are considered serious and meet the SAE criteria should be listed on the AE CRF page. When bleeding episodes that meet the SAE criteria are recorded on the AE CRF, the location (site) of the bleed and the etiologic classification as spontaneous or traumatic should be included (as described in Section 7.2.1 and Section 7.2.3). The subject diary or medical record will serve as the source document for bleeding episodes during the study. Investigators (or designee) and/or monitors will review the subject's diary/medical records to assist in classification if necessary.

7.2.3. Types of Bleeding

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

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

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

7.2.4. Location of Bleeds

For the purposes of this study, when subjects report a bleed treated with hemostatic therapy, the location of the bleed should be recorded in the subject diary or medical record. Bleeds will be reported as occurring in 1 of the following locations: joint, muscle/soft tissue, or other. Each individual location of multiple-site bleeds will be reported. For joint bleeds, the specific joint will be reported. Parameters to identify joint bleeds include: pain on joint motion, limitation of motion, and visible swelling of joint.

7.2.5. Treatment of Bleeding Episodes

Bleeding episodes that occur during this study may be treated (on-demand) with hemostatic therapy (eg intravenous factor products or rFVIIa bypass agent therapy at approximately 90 µg/kg) as deemed appropriate by the investigator. The specific treatment with hemostatic therapy is at the discretion of the 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 subject experiences a bleeding episode during the washout period preceding screening laboratory assessments, the subject is to be stabilized utilizing the subject'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 subject experiences a bleeding episode during the washout period preceding the initial administration of PF-06741086 the subject is to be stabilized utilizing the subject'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 subject experiences a bleeding episode during the PK assessment period following administration of PF-06741086, the subject is to be stabilized utilizing the subject's usual factor VIII or factor IX treatment regimen or rFVIIa bypass agent therapy at approximately 90 µg/kg, and protocol specified observations and procedures should proceed to completion. Pausing or withdrawal of treatment with investigational product is not required in the event of a breakthrough bleed, but may be considered at the discretion of the investigator.

7.3. Pharmacokinetics (PK)

7.3.1. Plasma for Analysis of PF-06741086

During all study periods, blood samples (4.5 mL) to provide approximately 1.5 mL plasma for PK analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities. During periods with IV dosing, the PK sample should be taken from the opposite arm from the IV dosing.

The actual times may change but the number of PK samples will remain the same. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Samples should be obtained within the time window specified in the Schedule of Activities; at the end of the IV infusion, samples obtained from 0 to 5 minutes after the end of the infusion will not be captured as a protocol deviation (6 or more minutes after the end of the infusion will be a deviation).

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the central lab manual.
- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, 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 sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.
- CCI [redacted]

7.3.2. Shipment of Pharmacokinetic Samples

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

7.4. Immunogenicity

7.4.1. Immunogenicity Analyses

The immunogenicity samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the immunogenicity processing steps, 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 sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

CCI [redacted]

7.4.2. Plasma for Analysis of ADA (Anti-PF-06741086) and NAb

During all study periods, blood samples (9.0 mL) to provide approximately 3.0 mL plasma for ADA and NAb analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities.

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

7.4.3. Shipment of Immunogenicity Samples

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

7.5. Pharmacodynamics

7.5.1. Pharmacodynamic Markers

The PD samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, 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 sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

CCI [redacted]

7.5.1.1. Samples for TFPI Level

During all study periods, blood samples (2.7 mL) to provide approximately 1.0 mL plasma for TFPI level analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities.

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

7.5.1.2. Samples for Thrombin Generation

During all study periods, blood samples (3.5 mL) to provide approximately 600 µL plasma for TGA analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities.

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

7.5.1.3. Samples for Prothrombin Fragment 1 and 2 and D-dimer

During all study periods, blood samples (4.5 mL) to provide approximately 250 µL plasma for PF1+2 analysis, approximately 1.0 mL for coagulation tests analyses (D-dimer along with the following safety laboratories: Fibrinogen, PT/INR, aPTT, Protein C, Protein S and ATIII), and remaining up to approximately 1.0 mL for back-up will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities.

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

7.5.1.4. Samples for Dilute Prothrombin Time

During all study periods, blood samples (2.7 mL) to provide approximately 200 µL plasma for dPT analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the Schedule of Activities.

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

7.5.2. Shipment of Pharmacodynamic Samples

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

CCI [redacted]

CCI [redacted]

[redacted]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[redacted]

7.7. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 389.3 mL for SC cohorts and 428.7 mL for IV cohorts (based on Screening through Day 113). The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected should not increase. 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 6. Blood Volume for SC Cohorts

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs					**157**
Serum chemistry (with Lipid profile[a])	5	1	7	1	45
Hematology	3	1	7	1	27
Prothrombin 20210 mutation	3	1	0	0	3
Factor V Leiden mutation testing	3.5	1	0	0	3.5
aPTT, PT/INR, Anti-thrombin III[b], Factor VIII and Factor IX activity[c], Fibrinogen, Protein C[a], Protein S[a], D-dimer, PF1+2 (PD samples) [Single combined sample]	4.5	1	11	1	58.5
Serology (HBs Ag, HBc Ab, HCV Ab, and HIV)	5	1	0	0	5
Cardiac Troponin I[d]	3	0	5	0	15
PK	4.5	0	11	1	**54**
Immunogenicity (ADA, NAb)	9	0	5	1	**54**
PD (note some PD assayed from safety samples)					**106.8**
TFPI level	2.7	0	11	1	32.4
TGA	3.5	0	11	1	42
dPT	2.7	0	11	1	32.4
Factor VIII and Factor IX inhibitor[a]	4.5	1	0	0	4.5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Banked biospecimens	4	0	1	0	**4**
TOTAL					**393.8**

[a] at Screening only.
[b] at Screening and Days 1, 8, 15, 22 and 29 only.
[c] at Screening and Day 1 only.
[d] at Days 1, 8, 15, 22 and 29 only.

Table 7. Blood Volume for IV Cohorts

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs					**161.5**
Serum chemistry (with Lipid profile[a])	5	1	7	1	45
Hematology	3	1	7	1	27
Prothrombin 20210 mutation	3	1	0	0	3
Factor V Leiden mutation testing	3.5	1	0	0	3.5
aPTT, PT/INR, Anti-thrombin III[b], Factor VIII and Factor IX activity[c], Fibrinogen, Protein C[a], Protein S[a], D-dimer, PF1+2 (PD samples) [Single combined sample]	4.5	1	12	1	63
Serology (HBs Ag, HBc Ab, HCV Ab, and HIV)	5	1	0	0	5
Cardiac Troponin I[d]	3	0	5	0	15
PK	4.5	0	15	1	**72**
Immunogenicity (ADA, NAb)	9	0	5	1	**54**
PD (note some PD assayed from safety samples)					**115.7**
TFPI level	2.7	0	12	1	35.1
TGA	3.5	0	12	1	45.5
dPT	2.7	0	12	1	35.1
Factor VIII and Factor IX inhibitor[a]	4.5	1	0	0	4.5
Exploratory biomarkers	2.7	0	5	0	**13.5**
Banked biospecimens	4	0	1	0	**4**
Discard tube	2	0	4	0	**8**
TOTAL					**433.2**

[a] at Screening only.
[b] at Screening and Days 1, 8, 15, 22 and 29 only.
[c] at Screening and Day 1 only.
[d] at Days 1, 8, 15, 22 and 29 only.

7.8. Triggered Requirements

Condition	Action
• Platelet count <75,000/μL. • Fibrinogen level < LLN. • Hemoglobin level <10 gm/dL. • PT/INR ≥1.25 times the ULN	Subjects who are found to have one of the coagulation pathway abnormalities defined by these corresponding lab value criteria should be brought into the clinic immediately for an unscheduled visit and the respective laboratory test should be repeated.
Positive ADA	Subjects may be requested to return for additional follow-up visits after Day 113. Extended follow-up visits every 2 weeks for up to 3 months, including vital signs, immunogenicity, AE and concomitant medication assessments, may be performed.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any nonserious AE that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;

- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.3.1. Adverse Events of Special Interest

PF-06741086 may increase the risk of formation of thrombi or emboli, and thus may increase the risk of AEs associated with thrombi or emboli. AEs that are associated with or reasonably suspected to be related to thrombi or emboli will require expedited reporting to the Sponsor as defined in Section 8.15.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject 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 participating subject.

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or Sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Hemophilia Events

Hemophilia events are certain AEs that are likely to occur due to the subject's hemophilia. For example, pain, swelling, or decreased range of motion due to a bleed may be an expected consequence of hemophilia (the bleeding episode itself is not reported as an AE, unless the bleeding episode meets the criteria for a Serious Adverse Event, see Section 8.7). Investigators should determine if an AE is expected because of the subject's hemophilia. Bleeding or bruising, not due to the subject's hemophilia, will be recorded as an AE, and not a hemophilia event. Hemophilia events that require hospitalization or meet other SAE criteria should be reported as SAEs.

8.7. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are 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.

8.7.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.7.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with 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).

  Concurrent with

  - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational 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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.8. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.9. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

Severity grading for dose limiting toxicities (≥ Grade 3), per Appendix 2, will follow the NIAID DMID scale.[7]

8.10. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. 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 (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.11. Exposure During Pregnancy

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

1. 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;

2. 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);

3. 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 study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an 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 subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) 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 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 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 investigator. 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 study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.12. 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 the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.13. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.14. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs.

8.15. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.15.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.15.2. Adverse Events of Special Interest

Thromboembolic or ischemic events are considered important medical events (see Section 8.7). As medically important events, Pfizer is to be notified within 24 hours of awareness of the thromboembolic or ischemic event. Data entry and additional reporting requirements will follow the same instructions for all other SAEs as listed in Section 8.15.1.

8.15.3. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.15.4. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

The total sample size of approximately 24 subjects for 4 dose cohorts is based on clinical considerations to provide adequate safety, tolerability, PK, PD and efficacy information at each dose level and/or route of administration. Each single dose cohort includes 6 subjects to ensure sufficient sample size for assessment of safety, PK, PD and efficacy. Additional subjects and/or cohorts may be added to fully explore the dose range and efficacy.

This sample size is also considered sufficient to support initial analyses for efficacy based on the endpoint of annualized bleeding rate (ABR). With 6 subjects per cohort, there is greater than 80% power to detect an 85% reduction in ABR compared to a historical factor-replacement treatment (control group) at one-sided alpha of 0.1. The power calculation is based on a Poisson regression model with assumptions that the historical control group has a bleeding rate of 2.36/patient-month and the study duration is 3 months.

9.2. Efficacy Analysis

9.2.1. Analysis of the Efficacy Endpoint

ABR will be calculated and summarized descriptively by dose level. ABR will also be summarized by inhibitor status, overall and by dose level and may be evaluated by factor deficiency (Factor VIII vs Factor IX).

The ABR will be analyzed using a Poisson regression model with over dispersion, if appropriate. The model based ABR and upper and lower 80% CI will be presented. The details will be included in the SAP.

9.3. Analysis of Pharmacokinetic Endpoints

For non-compartmental analysis (NCA) calculations with QW dosing frequency, the Day 36 plasma concentration will be imputed as the same as the Day 29 concentration.

The concentration of PF-06741086 will be descriptively summarized by PK dose and study day. Individual subject and median profiles of the PF-06741086 concentration versus time data will be plotted by dose using actual and nominal times respectively. Median profiles will be presented on both linear and logarithmic scales.

Noncompartmental PK parameters for PF-06741086 will be descriptively summarized by dose level and study day in accordance with Pfizer data standards.

Dose normalized AUC_{τ} and C_{max} of PF-06741086 will be plotted against dose (using a logarithmic scale), and will include individual subject values and the geometric means for each dose. These plots will be used to help understand the relationship between the PK parameters and dose.

9.4. Analysis of Pharmacodynamic Endpoints

The PD endpoints include total TFPI, thrombin generation (parameters include lag time, peak thrombin generation, and endogenous thrombin generation potential), prothrombin fragments 1+2, D-dimers, and dilute PT.

Absolute and change from baseline values will be listed and summarized descriptively by dose level and study day. Change from baseline of each PD endpoint will be analyzed using a mixed model for repeated measures (MMRM) with a restricted maximum likelihood method for the estimation of the covariance parameters. Details will be provided in the SAP.

dPT-concentration relationship will be explored. Dose-response relationship for other PD endpoints may also be explored.

CCI [redacted]

[redacted]

[redacted]

9.6. Safety Analysis

Adverse events, ECGs, vital signs (blood pressure, pulse rate, temperature and respiratory rate), physical examinations and safety laboratory data (including hematology, PT/INR, aPTT, chemistry, urinalysis, fibrinogen, anti-thrombin III activity and cardiac troponin I) will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Incidence and severity of TEAEs, withdrawals due to TEAEs, and infusion and injection site reactions will be summarized by dose level. Abnormal and clinically relevant changes in vital signs and ECG parameters will be summarized by dose level and study day. Incidence and magnitude of abnormal laboratory findings will be summarized by dose level. Abnormal safety findings will also be presented separately for inhibitor subjects by dose level.

Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay. Frequencies of ADA and NAb will be summarized by dose level and study day for samples collected.

Medical history, medication history and physical examination information, as applicable, collected during the course of the study will be captured for inclusion into the study database, unless otherwise noted. Any untoward findings identified on physical examination conducted after the administration of the first dose of investigational product will be captured as an adverse event, if those findings meet the definition of an adverse event. Data collected at Screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs and vital signs will be included in the study database. Demographic data collected at Screening will be reported.

9.6.1. Derivation of Vital Signs Parameters

Supine blood pressures and pulse rate will be recorded at each assessment time indicated in the Schedule of Activities. Baseline for vital signs will be defined as the last measurement before the Day 1 investigational product administration.

Vital signs (BP; PR) will be assessed for clinically relevant trends. The standard algorithms and reporting formats will be applied for analyzing all safety data.

Absolute values and changes from baseline in for systolic and diastolic blood pressure and pulse rate will be summarized by dose level and study day.

Maximum absolute values and maximum changes from baseline for vital signs will also be summarized descriptively by dose level using categories as defined in the SAP. Numbers and percentages of subjects meeting the categorical criteria will be provided and individual values listed in the study report.

9.6.2. Electrocardiogram (ECG) Analysis

Baseline for ECG will be defined as the mean of triplicate measurement before the Day 1 study drug administration. Changes from baseline for the ECG parameters QT interval, pulse rate, QTcF interval, PR interval and QRS interval will be summarized by dose level and study day.

The number (%) of subjects with maximum post dose QTc values and maximum increases from baseline in the following categories will be tabulated by dose level:

Safety QTcF

	Borderline (msec)	Prolonged (msec)
Absolute Value	≥ 450 - < 480	≥ 480
Absolute Change	30 - < 60	≥ 60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time post dose (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 three individual ECG tracings has a QTcF value ≥500 msec, but the mean of the triplicates is not ≥500 msec, the data from the subject's individual tracing will be described in a safety section of the study report 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 QTcF post dose from the average of the last pre-dose triplicate values on the dosing day in each period.

9.7. Interim Analysis

Cumulative data will be reviewed for dose escalation as defined in Section 3.3. The safety, PK, PD and efficacy data will be routinely reviewed by the study team for internal decisions regarding future study planning. Additional cohort(s) may be added, and a cohort may be expanded to fully explore the dose range and/or efficacy endpoint following the review of the cumulative data.

No formal interim analysis will be conducted for this study. However, as this is a Sponsor-open study, the Sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, facilitating PK/PD modeling, and/or to support clinical development. Unblinded results will be reviewed by a designated limited number of Sponsor colleagues within the study team. Refer to the study's Data Blinding Plan and/or SAP for specific details including delineation of study team members who will be involved in these unblinded reviews as well as steps to be instituted ahead of initiation of any unblinded review to ensure study integrity is maintained.

9.8. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC and national competent authority. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed and approved by the Sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject or his legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/Ecs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. 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 competent 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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06741086 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial 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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject 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 pre-specified 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II -– "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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7. NIAID Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Tables (available at https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf)

Abbreviations

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

Abbreviation	Term
ABR	annualized bleeding rate
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALB	albumin
ALT	alanine aminotransferase
APCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATIII	antithrombin III
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BU	Bethesda Units
CDC	complement dependent cytotoxicity
CDS	core data sheet
C_{max}	peak or maximum observed concentration
C_{min}	minimum observed concentration
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DMC	data monitoring committee
DNA	deoxyribonucleic acid
dPT	dilute prothrombin time
DU	dispensable unit
EC	ethics committee
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
EDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)

Abbreviation	Term
FEIBA	Factor Eight Inhibitor Bypass Agent
FIB	fibrinogen
FIH	first-in-human
FIX	coagulation factor IX
FIXa	activated factor X
FSH	follicle-stimulating hormone
FV	coagulation factor V
rFVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
GLOB	globulin
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBc Ab	hepatitis B core antibody
HBs Ag	hepatitis B surface antigen
HCV Ab	hepatitis C antibody
HIV	human immunodeficiency virus
Hr	hour
HRQL	health-related quality of life
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IgG1	immunoglobulin of the G isotype, subclass 1
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IPM	investigational product manual
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
IVR	interactive voice response
IWR	interactive web response
JET	jacketed external telemetry
KD	binding affinity
LFT	liver function test
LLN	lower limit of normal
LPD	local product document
LSLV	last subject last visit
MAD	multiple ascending dose
Min	minute

Abbreviation	Term
MMRM	mixed model for repeated measures
MTD	maximum tolerated dose
N/A	not applicable
NAb	neutralizing antibodies
NCA	non-compartmental analysis
NIAID DMID	National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases
NOAEL	no observed adverse effect level
PCD	primary completion date
PD	pharmacodynamic
PE	physical examination
PF1+2	prothrombin fragment 1+2
PFS	pre-filled syringe
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
PT/INR	prothrombin time/international normalized ratio
QM	once monthly, eg once every 28 days
QW	once weekly, eg once every 7 days
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCL	Supply Chain Lead
SIB	suicidal ideation and behavior
SOP	standard operating procedure
SPC	summary of product characteristics
SPR	surface plasmon resonance
SRSD	single reference safety document
TBD	to be determined
TEAE	treatment emergent adverse event
TEG	thromboelastography
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
TK	toxicokinetic
T_{max}	time to reach maximum concentration
TMDD	target mediated drug disposition
ULN	upper limit of normal
US	United States
USPI	United States package insert
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

Appendix 1. Thrombotic Adverse Events for Stopping Criteria

Acute coronary syndrome	Hepatic artery thrombosis	Retinal artery embolism
Acute myocardial infarction	Hepatic vascular thrombosis	Retinal artery occlusion
Aortic embolus	Hepatic vein thrombosis	Retinal artery thrombosis
Aortic thrombosis	Iliac artery embolism	Retinal vascular thrombosis
Arterial thrombosis	Intracardiac mass	Retinal vein occlusion
Atrial thrombosis	Intracardiac thrombus	Retinal vein thrombosis
Axillary vein thrombosis	Intracranial venous sinus thrombosis	Silent myocardial infarction
Basilar artery thrombosis	Intrapericardial thrombosis	Spinal artery embolism
Blue toe syndrome	Jugular vein thrombosis	Spinal artery thrombosis
Budd-Chiari syndrome	Mesenteric artery embolism	Splenic vein thrombosis
Carotid arterial embolus	Mesenteric artery thrombosis	Subclavian artery embolism
Carotid artery thrombosis	Mesenteric vein thrombosis	Subclavian artery thrombosis
Cavernous sinus thrombosis	Microembolism	Subclavian vein thrombosis
Cerebellar artery thrombosis	Myocardial infarction	Subendocardial ischaemia
Cerebellar embolism	Pelvic venous thrombosis	Superior sagital sinus thrombosis
Cerebral artery embolism	Penile vein thrombosis	Myocardial ischaemia
Cerebral artery thrombosis	Peripheral artery thrombosis	Thrombosis corpora cavernosa
Cerebral thrombosis	Peripheral embolism	Thrombosis mesenteric vessel
Cerebral venous thrombosis	Precerebral artery thrombosis	Thrombotic cerebral infarction
Cerebrospinal thrombotic tamponade	Portosplenomesenteric thrombosis	Thrombotic microangiopathy
Coronary artery embolism	Portal vein thrombosis	Thrombotic stroke
Coronary artery thrombosis	Pulmonary artery thrombosis	Transverse sinus thrombosis
Deep vein thrombosis	Pulmonary embolism	Truncus coeliacus thrombosis
Disseminated intravascular coagulation	Pulmonary microemboli	Vena cava embolism
Embolia cutis medicamentosa	Pulmonary thrombosis	Vena cava thrombosis
Embolic cerebral infarction	Pulmonary venous thrombosis	Vena caval embolism and thrombosis
Embolic stroke	Purpura fulminans	Venous thrombosis
Embolism	Renal artery thrombosis	Venous thrombosis limb
Embolism arterial	Renal embolism	Vertebral artery thrombosis
Embolism venous	Renal vascular thrombosis	
Femoral artery embolism	Renal vein embolism	
Hepatic artery embolism	Renal vein thrombosis	

Appendix 2. Criteria for Dose Limiting Toxicity

Adverse Events

Unless incontrovertibly due to extraneous causes, treatment emergent events conforming to the following criteria will constitute dose limiting toxicity:

1. Laboratory, vital sign or electrocardiogram findings conforming to the criteria provided below;

2. When not covered by the criteria listed below, treatment emergent adverse event graded as severe or ≥ Grade 3 under the NIAID Division of Microbiology and Infectious Diseases Adult Toxicity Tables (2007 Draft Version).

Hematology

Hemoglobin	<0.8 times the LLN or <80% times the baseline value if the baseline result is less than the lower limit of the reference range
Hematocrit	<0.8 times the LLN or <80% times the baseline value if the baseline result is less than the lower limit of the reference range
Platelets	<100,000 or ≤0.77 times the baseline value if the baseline result is less than the lower limit of the reference range.

Chemistry

Total bilirubin	>1.5 times the ULN
Direct bilirubin	>1.5 times the ULN
Indirect bilirubin	>1.5 times the ULN
Creatinine kinase	>2.0 times the ULN
Creatinine	>1.3 times the ULN

Coagulation Pathway

PT	≥4 seconds above the baseline value
Cardiac Troponin I	If values are normal at baseline, any results above the myocardial ischemia range Any result in the myocardial infarction range, regardless of baseline values

Fibrinogen	≤0.5 times LLN or ≤0.5 times the baseline value
Vital Signs	
Temperature	>38.5°C
Pulse Rate	<40 or >120 BPM
Blood Pressure	Systolic ≥30 mm Hg change from baseline in same posture
	Systolic <90 mm Hg
	Diastolic ≥20 mm Hg change from baseline in same posture
	Diastolic <50 mm Hg
Electrocardiogram	
PR interval	≥300 msec
	≥1.25 times baseline when baseline >200 msec
	≥1.50 times baseline when baseline ≤200 msec
QRS interval	≥140 msec
	≥1.50 times baseline
QTcF interval	≥500 msec