A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY, TOLERABILITY AND EFFICACY OF SUBCUTANEOUS PF-06741086 IN SUBJECTS WITH SEVERE HEMOPHILIA

Investigational Product Number:	PF-06741086
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2017-001255-31
Protocol Number:	B7841003
Phase:	2

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	08 November 2018	**General Changes Throughout Protocol** • Extension of treatment duration from 6 months to up to 365 days. • Editorial changes to fix titles, headers, grammar and typographical errors. **Protocol Summary** • Revised treatment duration from 6 months to up to 365 days. • Revised visit day numbers to correspond to up to 365 days treatment duration. **Schedule of Activities** • Added clinic visits on Day 225 (Month 8), Day 253 (Month 9), Day 281 (Month 10), Day 309 (Month 11), Day 337 (Month 12), and Day 365 (Month 13). • Revised Table 1 title and footnotes to correspond to additional clinic visits and extended treatment duration. **Section 1.2.4 B7841003 Study Rationale** • Revised treatment duration from 6 months to up to 365 days. **Section 2 Study Objectives and Endpoints** • Revised visit day numbers to correspond to up to 365 days treatment duration. **Section 3 Study Design** • Revised treatment duration from 6 months to up to 365 days.

		Section 3.2 Study Duration • Added clinic visits on Day 225 (Month 8), Day 253 (Month 9), Day 281 (Month 10), Day 309 (Month 11), Day 337 (Month 12), and Day 365 (Month 13). • Revised maximum study duration to 15 months (365 days for subjects continuing from study B7841002). **Section 4.1 Inclusion Criterion** • Revised Inclusion Criterion #2 for de novo subjects to add the requirement for episodic (on-demand) treatment prior to screening, as mandated by the FDA. • Added Inclusion Criterion #3 for de novo subjects to add the requirement for 6 or more breakthrough bleeding episodes in the 6 month period prior to screening, as mandated by the FDA. **Section 5.2 Subject Compliance** • Revised visit day numbers to correspond to up to 365 days treatment duration. **Section 5.3.2 Preparation and Dispensing** • Revised visit day numbers to correspond to up to 365 days treatment duration. **Section 6.2.3 Day 29 [±2 days], Day 57 [±5 days], Day 85 [±5 days], Day 113 [±7 days], Day 141 [±7 days], Day 169 [±7 days], Day 225 [±7 days], Day 253 [±7 days], Day 281 [±7 days], Day 309 [±7 days], Day 337 [±7 days], and Day 365 [±7 days] Visits** • Revised section to add clinic visits on Day 225, Day 253, Day 281, Day 309, Day 337, and Day 365. • Added text to clarify that Day 57 hematology

		and serum chemistry samples are for de novo subjects only. • CCI [redacted] • Revised visit day numbers to correspond to up to 365 days treatment duration. **Section 6.2.4 Day 393 [±7 days] – End of Study Visit** • Revised section to add clinic visit on Day 393. • Revised visit day numbers to correspond to up to 365 days treatment duration. **Section 7.8 Blood Volume** • Revised Table 4 to include additional samples.
Amendment 1	11 June 2018	**Title** • Removed "or Intravenous" as this route of administration will not be used in this study. **General Changes Throughout Protocol** • Editorial changes to fix titles, headers, grammar and typographical errors. **Protocol Summary** • Included subjects with inhibitors to FVIII or FIX. • Inclusion of adolescent subjects ≥12 to <18 years of age. **Schedule of Activities** • Screening:

		• Added assent/parental consent. • Added CD4 cell count lab. • Added Factor VIII or Factor IX inhibitor labs. Added footnote 'o' for instructions on inhibitor labs. • Added cardiac troponin I labs for de novo subjects from Day 1 to Day 29. • Updated footnote 'm' to add guidance on interim visits to perform IP administration or monitor self-administration. **Section 1.1 Mechanism of Action/Indication** • Included subjects with inhibitors to FVIII or FIX. **Section 1.2.3 Clinical Experience with PF-06741086** • Included subjects with inhibitors to FVIII or FIX. • Added text to indicate that interim clinical data from B7841002 may be found in the PF-06741086 Investigator's Brochure. **Section 1.2.5 Dose Rationale** • Added text to clarify dose assignments based on results from study B7841002. **Section 1.2.6 Summary of Risk/Benefit** • Included subjects with inhibitors to FVIII or FIX. **Section 2 Study Objectives and Endpoints** • Included subjects with inhibitors to FVIII or FIX. **Section 3 Study Design**

		• Included subjects with inhibitors to FVIII or FIX. • Figure 1 was updated to clarify dose assignments based on results from study B7841002. **Section 3.2 Study Duration** • Editorial changes and clarifying text added regarding visit windows, visit requirements, and the use of unscheduled visits. **Section 4.1 Inclusion Criteria** • Included subjects with inhibitors to FVIII or FIX. • Inclusion of adolescent subjects ≥12 to <18 years of age. • Removal of requirements for episodic treatment and 6 or more breakthrough bleeds prior to study entry. **Section 4.2 Exclusion Criteria** • Included subjects with inhibitors to FVIII or FIX. • An exclusion criterion regarding known severe hypercholesterolemia was added to comply with competent authority/ethics committee requests in France and Switzerland. **Section 4.3 Randomization Criteria** • Included subjects with inhibitors to FVIII or FIX. **Section 5 Study Treatments** • Removal of 100 mg/mL concentration from the study.

		Section 5.3.1 Dosage Form(s) and Packaging • Removal of 100 mg/mL concentration from the study. **Section 5.4 Administration** • Editorial changes to clarify SC administrations. **Section 5.7.1 Prohibited Medications** • Included subjects with inhibitors to FVIII or FIX. • Restrictions on rFVIIa dose level and prohibition of FEIBA conforms to study B7841002. **Section 5.7.2 Treatment(s) for Acute Bleeding Episodes** • Included subjects with inhibitors to FVIII or FIX. **Section 6.1 Screening** • Included subjects with inhibitors to FVIII or FIX. • Inclusion of adolescent subjects ≥12 to ≤18 years of age. • Added assent/parental consent. • Added CD4 cell count. • Added Factor VIII or Factor IX inhibitor labs (for subjects with hemophilia. **Section 6.2.1 Day 1 Visit** • Included subjects with inhibitors to FVIII or FIX. **Section 7.1.1 Laboratory Tests**

		• Included subjects with inhibitors to FVIII or FIX. • Editorial change to add CD4 cell count to table. **Section 7.1.3 Blood Pressure and Pulse Rates** • Editorial change to remove the term "intravenous" which was not part of the final study design. **Section 7.2.5 Blood Pressure and Pulse Rates** • Inclusion of subjects with inhibitors to FVIII or FIX. CCI [redacted] **Section 7.8 Blood Volume** • Updated maximum total blood volume in Table 4. **Section 9 Data Analysis/Statistical Methods** • Editorial changes regarding statistical hypothesis testing and safety analysis.
Original Version	17 April 2017	N/A

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 B7841003 is a Phase 2, open-label 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 and efficacy of long-term prophylaxis with 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 in subjects with hemophilia.

Subjects that complete study B7841002, a 3-month Phase 1b/2 study of prophylaxis treatment with PF-06741086, are eligible to enroll into this study to continue prophylaxis treatment. Study B7841003 will assess the safety, tolerability and efficacy of PF-06741086 up to a 365-day treatment period at the lowest dose level determined to be safe and efficacious in study B7841002.

Severe hemophilia A or B patients (FVIII or FIX activity ≤1%), including subjects with inhibitors to FVIII or FIX, who did not participate in study B7841002 will also be eligible for enrollment in B7841003. Two cohorts of subjects (6 subjects per cohort) will be enrolled to provide supplemental long-term safety, tolerability, and efficacy data on PF-06741086 in a de novo population. De novo cohorts will be open to the enrollment of adolescent severe hemophilia patients (≥12 to <18 years of age) and severe hemophilia patients with inhibitors to FVIII or FIX. After all subcutaneous (SC) cohorts have completed 3 months of treatment in study B7841002, the de novo subjects will be considered for enrollment into B7841003. All de novo subjects will be assigned to treatment with PF-06741086 for a treatment period of up to 365 days, at the lowest dose level determined to be safe and efficacious in B7841002.

During the 365-day treatment period, PF-06741086 will be administered subcutaneously. All subjects will be required to attend monthly clinic visits during the 365-day treatment period (Day 1 to Day 365) and one month follow-up (Day 393). CCI [redacted] Subjects who completed study B7841002 will be allowed to self-administer treatment at home after training by the site and demonstration of ability to self-administer by the subject. De novo subjects will be allowed to self-administer following the Day 29 visit, after training by the site and demonstration of ability to self-administer by the subject.

Through Day 365data will be reviewed to determine if PF-06741086 is safe and well tolerated at the respective dose levels. Dosing of any subject may be stopped if available data indicate that the treatment is not safe and well-tolerated.

Up to 36 subjects are planned to be treated in study B7841003 (24 subjects from B7841002 and 12 additional de novo subjects). Subjects will participate in the study for up to 15 months, including screening and follow-up.

There is no formal statistical hypothesis planned for testing in B7841003. 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 the number of subjects enrolled in study B7841002, and on clinical considerations to balance the need to minimize exposure of study subjects to the investigational product with the need to provide adequate safety and tolerability data for clinical development.

Safety endpoints will include treatment emergent adverse events, infusion/injection site reactions, safety CCI laboratory parameters. Prophylaxis efficacy will be assessed by collecting the number of acute bleeding episodes per subject during the treatment period of up to 365 days and determining the annualized bleed rate (ABR). For subjects continuing from study B7841002 on the same dose, these data may be combined between the studies to determine the ABR. All data will be summarized descriptively for each cohort and the overall study.

Demonstration of safety, tolerability and efficacy that supports long-term chronic treatment on an acceptable dosing schedule is intended to support 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 table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Screening, Day 1 to Day 393, All Subjects

Protocol Activity	Screening	Clinic Visits														End of Study Visit[d]
Visit Identifier[a]	Screening[b]	Day 1[c]	Day 29 (Month 1)	Day 57 (Month 2)	Day 85 (Month 3)	Day 113 (Month 4)	Day 141 (Month 5)	Day 169 (Month 6)	Day 197 (Month 7)	Day 225 (Month 8)	Day 253 (Month 9)	Day 281 (Month 10)	Day 309 (Month 11)	Day 337 (Month 12)	Day 365 (Month 13)	Day 393 (Month 14)
Visit window	Day -34 to Day -1	+ 1 day	±2 day	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Informed consent or Assent/ Parental consent	X	X[c]														
Medical history (including hemophilia history and inhibitor history, and bleeding episodes over past 6 months)[e]	X	X														
Medication history	X	X														
Demography, Height, Weight	X															X (weight)
Full physical examination	X															X
Limited physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Screening, Day 1 to Day 393, All Subjects

Protocol Activity	Screening	Clinic Visits														End of Study Visit[d]
Visit Identifier[a]	Screening[b]	Day 1[c]	Day 29 (Month 1)	Day 57 (Month 2)	Day 85 (Month 3)	Day 113 (Month 4)	Day 141 (Month 5)	Day 169 (Month 6)	Day 197 (Month 7)	Day 225 (Month 8)	Day 253 (Month 9)	Day 281 (Month 10)	Day 309 (Month 11)	Day 337 (Month 12)	Day 365 (Month 13)	Day 393 (Month 14)
Visit window	Day -34 to Day -1	+ 1 day	±2 day	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Contraception instructions/ check[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[i]	X	X			X			X			X				X	
ECG	X[b]	X[b]	X[b]													
Serum chemistry[j]	X	X	X[b]	X[b]	X			X			X				X	
Hematology[j]	X	X	X[b]	X[b]	X			X			X				X	
CD4 cell count	X															
[redacted]			[redacted]	[redacted]		[redacted]			[redacted]			[redacted]				[redacted]	
Fibrinogen	X	X[b]			X			X			X				X	
[redacted]		[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			[redacted]				[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]		[redacted]			[redacted]			[redacted]				[redacted]	
Prothrombin time (PT)		X	X[b]		X			X			X				X	
Cardiac troponin I		X[b]	X[b]													
Factor VIII and Factor IX activity	X	X			X			X			X				X	
Factor VIII or Factor IX inhibitor levels (for subjects with a hemophilia history of inhibitor only)	X[b,o]															

Table 1. Screening, Day 1 to Day 393, All Subjects

Protocol Activity	Screening	Clinic Visits														End of Study Visit[d]
Visit Identifier[a]	Screening[b]	Day 1[c]	Day 29 (Month 1)	Day 57 (Month 2)	Day 85 (Month 3)	Day 113 (Month 4)	Day 141 (Month 5)	Day 169 (Month 6)	Day 197 (Month 7)	Day 225 (Month 8)	Day 253 (Month 9)	Day 281 (Month 10)	Day 309 (Month 11)	Day 337 (Month 12)	Day 365 (Month 13)	Day 393 (Month 14)
Visit window	Day -34 to Day -1	+ 1 day	±2 day	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Prothrombin 20210 mutation testing	X															
Factor V Leiden mutation testing	X															
Lipid profile[i]	X															
Protein C activity/Protein S level/ATIII activity	X															
Serology: HBs Ag, HBc Ab, HCV Ab and HIV	X															
[redacted]		[redacted][cc]	[redacted]		[redacted]			[redacted]			[redacted]				[redacted]	
[redacted]	[redacted]															
[redacted]		[redacted]	[redacted]		[redacted]			[redacted]			[redacted]				[redacted]	
Inclusion/ exclusion criteria review	X	X														
Treatment assignment		X														
Investigational Product administration (SC)		X	Weekly administration at home or in clinic[m] →	→	→	→	→	→	→[m]	→	→	→	→	→[m]		
Subject diary[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Screening, Day 1 to Day 393, All Subjects

Protocol Activity	Screening	Clinic Visits														End of Study Visit[d]
Visit Identifier[a]	Screening[b]	Day 1[c]	Day 29 (Month 1)	Day 57 (Month 2)	Day 85 (Month 3)	Day 113 (Month 4)	Day 141 (Month 5)	Day 169 (Month 6)	Day 197 (Month 7)	Day 225 (Month 8)	Day 253 (Month 9)	Day 281 (Month 10)	Day 309 (Month 11)	Day 337 (Month 12)	Day 365 (Month 13)	Day 393 (Month 14)
Visit window	Day -34 to Day -1	+ 1 day	±2 day	±5 days	±5 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Collect number of new bleeding episodes		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Monitoring injection site reactions		X	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Serious and non-serious adverse event monitoring		X	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Concomitant treatments		X	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: → = ongoing/continuous event; CCI ; 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; CCI ; PT/INR = prothrombin time/international normalized ratio; CCI .

a. Day relative to start of study treatment (Day 1).

b. Screening and additional activities noted apply to de novo subjects who did not participate in B7841002. Please see Section 6 for additional details.

c. For subjects who completed study B7841002, informed consent procedures will occur at the Day 1 visit. The Day 1 visit for B7841003 may occur on the same day (same visit to the clinic) as the B7841002 Day 85 or Day 113 visit.

All Day 1 (or B7841002 Day 85 or Day 113) blood draws must be done prior to administration of IP.

The following conditions apply to all Day 1 activities:

- Inclusion/exclusion criteria: Criteria should be reviewed (and eligibility confirmed) at Day 1 for subjects who completed B7841002 more than 30 days prior to the scheduled Day 1 visit. Please see Section 6.1 for required procedures.
- Treatment assignment: All subjects will be required to receive a new subject number for this study. Other procedures for treatment assignment may not be necessary for subjects who completed study B7841002.

d. See Section 6.2.5 for guidance on follow-up contact, if necessary.

e. Medical history data for subjects from study B7841002 will also be used for subjects enrolling into B7841003. Resolved AEs from B7841002 may be entered as additional medical history, where applicable.

f. At Day 1 through Day 365, 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.

g. Instructions will be provided at Screening and Day 1 visit; contraception check will be performed at other visits.

h. Vital signs to be assessed include pulse rate, respiratory rate, oral temperature, and blood pressure (supine).

i. See Section 7.1.1, Table 3, for list of analytes. Differential hematology panel required at Days 1, 85, 169 and 337.

[redacted]

m. Prior to self-administration, sites must ensure subjects are trained on IP administration and storage per the IP manual. Dosing between planned clinic visits may be administered by investigational site staff until the respective subject has been properly trained in self-administration. Sites should follow-up (eg, via phone call) to ensure compliance with administration instructions, where necessary. Subjects who completed the Day 197 (Month 7) visit prior to Amendment 2 (and extension of treatment duration) are allowed to restart treatment, beginning with Day 225 (Month 8). Hematology, chemistry, and urinalysis results from Day 169 (Month 6) should be reviewed against inclusion/exclusion criteria prior to the resumption of treatment to ensure there are no exclusionary laboratory abnormalities. Day 337 (Month 12) will be the final visit where IP is dispensed for self-administration. For subjects being dosed in the clinic, 7 days before Day 365 is the final day for dosing.

n. 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.

o. 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. Day 2 through Day 22: CCI and Treatment Visits for De Novo Subjects

Protocol Activity	Clinic Visits				
Visit Identifier[a]	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 22**
Visit window	**±1 day**	**±1 day**	**±2 day**	**±2 day**	**±2 days**
Limited physical examination	X	X	X	X	X
Contraception instructions/check	X	X	X	X	X
CCI					
Serum chemistry			X	X	X
Hematology			X	X	X
Prothrombin time (PT)			X	X	X
Cardiac troponin I			X	X	X
CCI					
Investigational Product administration (SC)			X[b]	X[b]	X[b]
Subject diary[c]			X	X	X
Collect number of new bleeding episodes	→	→	→	→	→
Monitoring injection site reactions	→	→	→	→	→
Adverse event monitoring	→	→	→	→	→
Concomitant treatments	→	→	→	→	→

Abbreviations: → = ongoing/continuous event; CCI

a. Day relative to start of study treatment (Day 1).

b. IP administration on Day 8, Day 15, and Day 22 to occur at the clinic with training on IP self-administration for de novo subjects.

c. Subject diary dispensed and/or collected. Subject diary is reviewed, including information about study compliance, investigational product infusions, 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 B7841003 is a long-term study on the safety, tolerability and efficacy of PF-06741086 during up to 365 days of treatment. Satisfactory safety, tolerability, and efficacy data from this study are intended to support the development of PF-06741086 as a treatment in hemophilia.

1.2. Background and Rationale

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 intravenous (IV) administration route and frequency of infusion required for effective prophylaxis treatment remains burdensome, and may result in reduced adherence to the treatment schedule 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 and was in the low-nanomolar to sub-nanomolar range. 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. 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. Combined, repeated dose administration of PF-06741086 at 50 mg/kg and NovoSeven RT at 3 mg/kg to rats was associated microscopically with an increased incidence and/or severity of minimal to mild, acute thrombi/emboli in the lung and injection site (tail) without any microscopic evidence of secondary tissue injury or effects on the animals' clinical condition in the main study animals. These findings were not observed with the same incidence/severity with either test article administration at the same doses alone or in combination when administered as PF-06741086 at 50 mg/kg and NovoSeven RT at 0.8 (0.4 BID) mg/kg indicating a greater effect of combined administration of PF-06741086 and NovoSeven RT at 50 and 3 mg/kg, respectively. Administration of Novoseven RT at any dose alone or in combination with PF-06741086 resulted in test article-, non-dose-related lower group means for PT. The magnitude of the change was not significantly altered by co-administration of PF-06741086. Thrombi/emboli formation and shortening of PT are consistent with the pharmacology of both test articles. There was 1 test article-related unscheduled moribund euthanasia of an animal in the PF-06741086 (50 mg/kg)/NovoSeven RT (3 mg/kg)-dose pharmacokinetic group on Day 8 within 2 hours of the first Novoseven RT dose because of bilateral hindlimb paralysis related to acute thrombi/emboli in the iliac arteries; acute thrombi/emboli were also observed in other tissues. This animal also had ileal and cecal erosions of uncertain etiology, which may have contributed to the animal's hypercoagulable state. The systemic exposure of NovoSeven RT observed in rats at 0.4, 1, and 3 mg/kg was equivalent or greater than the

predicted clinical exposure of NovoSeven RT at 30, 90, and 270 µg/kg respectively. In addition, the observed daily total exposure of NovoSeven RT at 0.8 (0.4 BID) mg/kg in rats was approximately equivalent to the predicted total daily clinical exposure after 3 doses of NovoSeven RT at 90 µg/kg. Systemic exposures characterized by C_{max} and AUC_t for PF-06741086 and NovoSeven RT were not affected by combined test article administration.

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.

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 of up to 6 or 3 months in duration, respectively. 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. This nonclinical program is intended to support clinical trials of up to 3 months in duration.

PF-06741086 was administered to rats and monkeys by intravenous (IV) and subcutaneous (SC) injection, in studies up to 26 weeks in duration. When administered weekly to rats for 26 weeks at doses up to 1000 mg/kg/dose, the no observed adverse effect level (NOAEL) was 1000 mg/kg/dose, corresponding to a C_{max} of 29,800,000 ng/mL and an AUC_{168} of 1,840,000,000 ng·h/mL. In rats, at 1000 mg/kg/dose IV, C_{max} (29,800,000 ng/mL) and AUC_{168} (1,840,000,000 ng•h/mL) on Day 176 were 95x and 69x the predicted human exposure at the highest intended IV dose of 1000 mg once monthly (QM) (C_{max} = 313,000 ng/mL and AUC_{168} = 26,600,000 ng•h/mL). When administered once weekly for 13 weeks, the no observed adverse effect levels (NOAELs) were 1000 mg/kg/dose IV and 180 mg/kg/dose SC in rats and 500 mg/kg/dose IV and 90 mg/kg/dose SC in monkeys. In rats, at 1000 mg/kg/dose IV, C_{max} (27,800,000 ng/mL) and AUC_{168} (1,940,000,000 ng•h/mL) on Day 85 were 89x and 73x the predicted human exposure at the highest intended IV dose and at 180 mg/kg/dose SC, C_{max} (416,000 ng/mL) and AUC_{168} (45,300,000 ng•h/mL) on Day 85 were 3x and 2x the predicted human exposure at the highest intended SC dose of 450 mg once weekly (QW) (C_{max} = 134,000 ng/mL and AUC_{168} = 21,500,000 ng•h/mL). In monkeys, at 500 mg/kg/dose IV, C_{max} (18,400,000 ng/mL) and AUC_{168} (2,000,000,000 ng•h/mL) on Day 85 were 59x and

75x the predicted human exposure at the highest intended IV dose and at 90 mg/kg/dose SC, C_{max} (2,480,000 ng/mL) and AUC_{168} (364,000,000 ng•h/mL) on Day 85 were 19x and 17x the predicted human exposure at the highest intended SC dose. Anticipated staining in the endothelium and placental decidual cells and trophoblasts was observed in the tissue cross reactivity assay. In the C1q binding and FcR binding assays, PF-06741086 did not bind to C1q, suggesting an inability to activate the classical complement pathway and induce CDC, and FcR binding assays showed that PF-06741086 had low potential to elicit ADCC activity. In the cytokine release assay, PF-06741086 did not elicit a test article-related release of TNF α, IL-6, or IFN-γ. When administered to rats as a single SC dose of 300 mg/kg, the NOAEL in the 1-day local toleration study with a 1-week recovery was 300 mg/kg SC, corresponding to a C_{max} (1,390,000 ng/mL) and AUC_{168} (139,000,000 ng•h/mL) with 10x and 7x the predicted human exposure at the highest intended SC dose. 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.

1.2.3. Clinical Experience with PF-06741086

To date, a single clinical study has been completed with PF-06741086. The clinical development of PF-06741086 began with study 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, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity were collected during clinic confinement (7 days) and outpatient follow-up (up to 84 days).

In study B7841001, there were no significant adverse effects following single dose administration with PF-06741086. There were no serious adverse events (SAEs). There were no severe adverse events (AEs). There were no clinically significant changes in laboratory parameters. Additional clinical information regarding PF-06741086 including data from study B7841001 may be found in the Investigator Brochure.

The second clinical investigation of PF-06741086 is ongoing with study B7841002, an open-label, Phase 1b/2, multiple ascending dose (MAD) study in severe hemophilia A or B, with or without inhibitors to FVIII or FIX. 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.

The primary objective of study B7841002 is to evaluate the safety and tolerability of multiple ascending doses of PF-06741086 administered by the SC. 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. It is expected that at least one dose level in study B7841002 will achieve prophylaxis efficacy outcomes sufficient to support further clinical development, including study B7841003.

Interim clinical data from study B7841002 may be found in the PF-06741086 Investigator Brochure.

1.2.4. B7841003 Study Rationale

The clinical investigation of PF-06741086 will continue with study B7841003, a long-term study on the safety, tolerability and efficacy of PF-06741086 up to 365 days of treatment. The primary objective of study B7841003 is to evaluate the safety and tolerability of long-term (up to 365 days) prophylaxis with PF-06741086 administered by the SC route. The secondary objective is the assessment of clinical efficacy based on the frequency of bleeding episodes. CCI [redacted]

Safety data including treatment-emergent AEs and laboratory abnormalities will be reviewed throughout the study to monitor any unanticipated risks associated with PF-06741086 treatment. Demonstration of safety, tolerability and efficacy that is supportive for long-term chronic treatment on an acceptable dosing schedule is intended to support progression of PF-06741086 to subsequent investigations in patients with severe hemophilia A or B.

1.2.5. Dose Rationale

Subjects enrolling in B7841003 from Cohort 1 (300 mg SC) of B7841002 will continue with their assigned dose level at the completion of B7841002. All other subjects enrolling in study B7841003 (following participation in B7841002) will receive the lowest SC dose level determined to be safe and efficacious in study B7841002 for the respective hemophilia population: 300 mg SC loading dose on Day 1, followed by 150 mg SC QW for non-inhibitor subjects; 300 mg SC QW for inhibitor subjects. De novo subjects in Cohort 5 (adolescents with or without inhibitors) and Cohort 6 (adults with inhibitors) will receive a 300 mg SC loading dose on Day 1, followed by 150 mg SC QW.

All doses will be administered by the SC route.

1.2.6. Summary of Risk/Benefit

Based on the potential risks, subjects will be monitored for treatment emergent events using parameters that include: serum chemistry, hematology, urinalysis; vital signs; physical examinations; 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 has been demonstrated at all tested single dose levels in the B7841001 FIH study. Further safety and tolerability testing is ongoing in the 3-month B7841002 study in subjects with hemophilia. Subjects continuing on to study B7841003 from B7841002 will only be allowed to do so at a dose level and route of administration that was determined to be safe and well-tolerated in study B7841002. De novo subjects enrolling in study B7841003 will only be assigned to PF-06741086 treatment at the lowest SC dose level determined to be safe and efficacious for the respective hemophilia population (non-inhibitor or inhibitor) in study B7841002. Further, de novo subjects will only be eligible for enrollment following completion of all SC cohorts through 3 months of treatment in B7841002.

Possible risks from long-term 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 low 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 treatment with FVIII or FIX replacement. 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.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigators Brochure.

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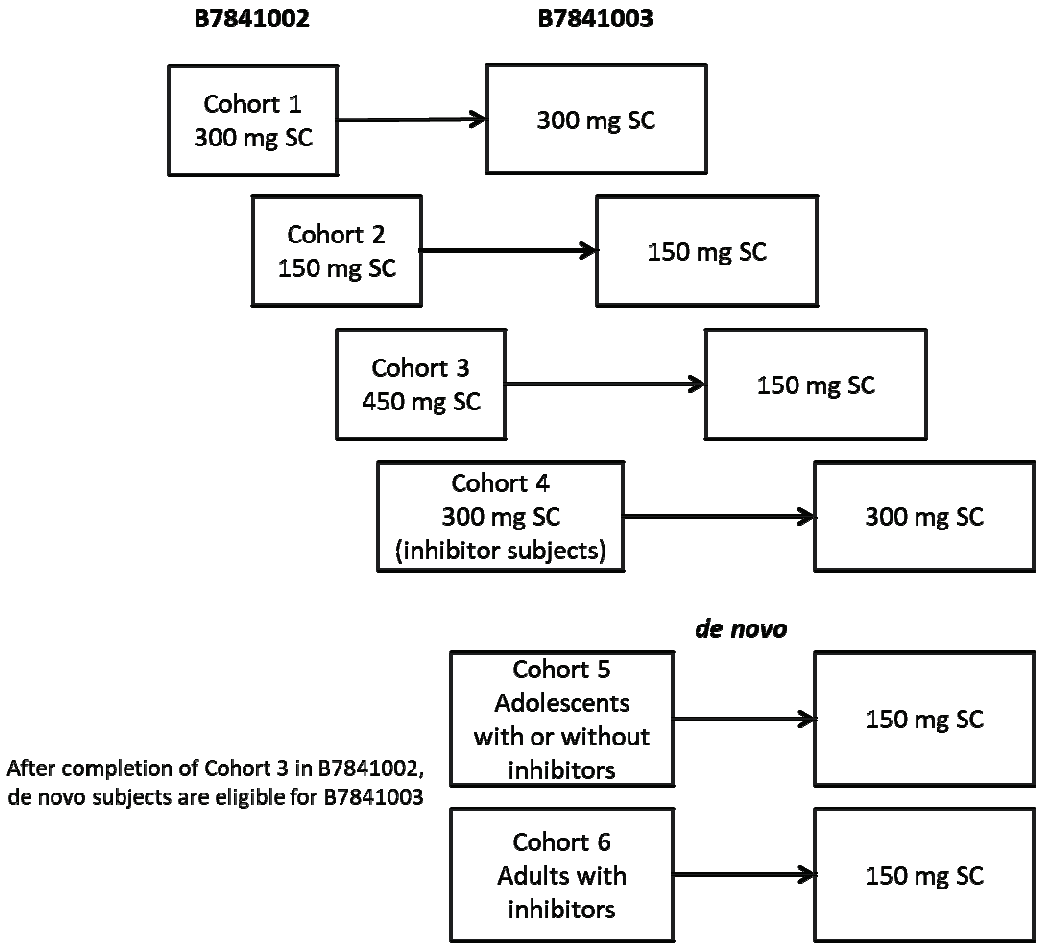
2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To determine the safety and tolerability of long-term treatment (up to 365 days) with PF-06741086 in severe hemophilia A and B subjects with or without inhibitors to FVIII or FIX.	• Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs); Day 1 up to Day 393. • Frequency and magnitude of abnormal laboratory findings (including hematology, chemistry, urinalysis); Day 1 up to Day 393. • Changes from baseline in vital sign (blood pressure, pulse rate, temperature and respiration rate) measurements and physical examinations; Day 1 up to Day 393 and ECG Day 1 to Day 29 in de novo subjects only. • Frequency, severity and casual relationship of infusion and injection site reactions; Day 1 up to Day 393.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To determine the efficacy of long-term treatment with PF-06741086 in severe hemophilia A and B subjects with or without inhibitors to FVIII or FIX.	• Frequency and annualized rate of bleeding episodes; Day 1 up to Day 393. • Frequency of rescue (FVIII, or FIX) therapy for treatment of breakthrough bleeding episodes.
Tertiary/Exploratory Objective(s):	**Tertiary/Exploratory Endpoint(s):**
[redacted]	[redacted]

3. STUDY DESIGN

B7841003 is an open-label long-term (treatment of up to 365 days) evaluation of PF-06741086 as a prophylactic treatment regimen in subjects with hemophilia A or B, with or without inhibitors to FVIII or FIX. Investigators, subjects, site staff and sponsor study team members will not be blinded to treatment assignment. Subjects will be assigned to treatment cohorts as indicated in Figure 1 below.

Figure 1. B7841003 Dose Assignment



Subjects enrolling in B7841003 from Cohort 1 (300 mg SC) of B7841002 will continue with their assigned dose level at the completion of study B7841002. All other subjects enrolling in B7841003 will receive the lowest dose level determined to be safe and efficacious for the respective hemophilia population in study B7841002.

Subjects who complete study B7841002 may enroll immediately into study B7841003 at the B7841002 Day 85 or Day 113 visit. This visit will be Day 1 for the B7841003 Schedule of Activities. Procedures that are required at the B7841002 Day 85 or Day 113 visit do not need to be repeated for B7841003 Day 1.

All subjects who complete study B7841002 are eligible for study B7841003, unless a specific exclusion criterion in Section 4.2 is noted at the Day 1 visit. It is expected that some subjects who complete B7841002 may not be able to immediately enroll in B7841003. These subjects do not require a complete re-screening, however if there is a 30-day or longer gap between the B7841002 last study visit and the B7841003 Day 1 visit, the investigator must review the criteria in Section 4.1 and Section 4.2, perform the limited set of procedures listed in Section 6.1 and confirm that the subject still meets eligibility criteria.

Subjects who completed the Day 197 (Month 7) visit prior to Amendment 2 (and extension of treatment duration) are allowed to restart treatment, beginning with Day 225 (Month 8). Hematology, chemistry, and urinalysis results from Day 169 (Month 6) should be reviewed against inclusion/exclusion criteria prior to the resumption of treatment to ensure there are no exclusionary laboratory abnormalities.

De novo subjects will be eligible for enrollment following completion of all subcutaneous cohorts (ie, after Cohort 3) through 3 months of treatment in B7841002.

Dosing of any subject may be stopped if available data indicate that the treatment is not safe and well-tolerated.

3.1. Planned Number of Subjects

Approximately 36 subjects (24 subjects from B7841002 and 12 additional de novo subjects) are planned for enrollment at approximately 20 study sites.

3.2. Study Duration

Subjects who completed B7841002 within 30 days of B7841003 Day 1 will begin this study at Day 1 (no Screening visit). A limited Screening visit and eligibility criteria review is required prior to Day 1 for subjects who completed study B7841002 more than 30 days prior to the scheduled Day 1 visit.

All Screening activities apply to de novo subjects who did not participate in B7841002. Screening procedures may be completed up to 35 days prior to the Day 1 visit for these subjects (ie, Day -34).

All subjects that meet inclusion/exclusion criteria at Day 1 will be assigned to a treatment regimen and dosed. All subjects will return for clinic visits on Day 29, Day 57, Day 85, Day 113, Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, Day 337, Day 365 with follow-up and end-of-study procedures on Day 393. De novo subjects will undergo additional visits, as per Table 2 during the interval between Day 1 and Day 29. The total duration of the treatment period will be up to 365 days.

Subjects not yet proficient in SC self-administration may have scheduled doses of PF-06741086 administered by investigational site staff or their properly trained designees during the interval(s) between planned study visits.

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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 subject who completed B7841002 will be approximately 14 months (excluding screening and any interruption in treatment prior to approval of Amendment 2). The maximum total duration of the study for de novo subjects, from initial screening to final follow-up, will be approximately 15 months.

3.3. Dose Modification Rules for Adverse Events

Dosing may be stopped, paused, or modified based on the following criteria:

- Dosing at the current dose level (or higher dose levels) will be paused for any treatment emergent thrombotic event (see Appendix 2 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.
- Dosing will be paused (and may resume at a lower dose after sponsor review of safety data) if a subject experiences a treatment emergent severe or ≥ Grade 3 adverse event without resolution after repeat administration with PF-06741086, unless incontrovertibly due to extraneous causes.

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 8.2.3 for qualifying events).

3.3.1. Dose Modification Rules for Breakthrough Bleeding Episodes

Dosing may be modified to the next higher permitted dose level (based on study B7841002 safety results) if a subject experiences increased breakthrough bleeding frequency that meets the following criteria:

- Two spontaneous (atraumatic) bleeding episodes into major joints such as elbow, ankle or knee joint(s) and/or other target joints over a 4 week (28 day) period.

OR

- Three or more spontaneous (atraumatic) bleeding episodes (eg, 1 joint and 2 soft tissue or other site) over a 4 week (28 day) period.

4. SUBJECT ELIGIBILITY CRITERIA

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.

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

4.1. Inclusion Criteria

All subjects must meet the following inclusion criteria to be eligible for enrollment into the study. Subjects continuing from B7841002 within 30 days of the B7841003 - Day 1 visit do not require screening procedures to confirm eligibility:

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 <75 years of age.
3. Body Mass Index (BMI) ≥17.5 and ≤30.5 kg/m^2 and total body weight ≥50 and ≤100 kg.
    a. For adolescents, the BMI must be ≥14 kg/m^2 and total body weight must be ≥30 kg.
4. Diagnosis of severe hemophilia A or B (FVIII or FIX activity ≤1%).
5. 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).
6. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

The following inclusion criteria only apply to de novo subjects (Cohorts 5 and 6) only:

1. Adolescent males ≥12 to <18 years of age are eligible.
2. Patients with an episodic (on-demand) treatment regimen 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 activated prothrombin complex concentrate [APCC]: at least 72 hours; for other products: at least 5 half-lives) prior to Screening laboratory assessments of factor activity and have no plans to institute prophylactic factor or bypass agent treatment during the study period.

3. 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.

4. 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.

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, or known severe, uncontrolled hypercholesterolemia.

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

6. 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.

7. Abnormal renal or hepatic function as defined by the following laboratory results at any time prior to Day 1:

   - 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 any time prior to Day 1:

   - 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 any time prior to Day 1:
   - Prothrombin time (PT) >1.25 times the ULN.
10. CD4 cell count ≤200/μL.
11. Known hypersensitivity (eg, latex allergy) or allergic reaction to hamster protein.
12. Known sensitivity to heparin or heparin induced thrombocytopenia.
13. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.
14. Participation in other studies involving investigational drug(s) (excluding PF-06741086) within 30 days prior to study entry and/or during study participation.
15. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
16. Fertile male subjects 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 (applies only to de novo subjects).

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. All subjects will be required to receive a new subject number for this study. Other procedures for treatment assignment may not be necessary for subjects who completed study B7841002.

Subjects will be assigned a randomization number provided they have satisfied all eligibility criteria and the following enrollment criteria:

1. De novo subjects in B7841003 must washout from FVIII (for at least 72 hours) or FIX (for at least 96 hours) replacement therapy 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 FVIII or FIX replacement therapy within 72 hours or 96 hours, respectively, or rFVIIa or APCC (eg, FEIBA) bypass agent therapy within 72 hours (or for other products: 5 half-lives) 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 Requirements

4.4.1. Contraception

All fertile male subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. A longer duration of contraception usage may be required if data 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 will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or 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 or the 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 (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female 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 copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (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 postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

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 product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator 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).

For this study, the investigational product(s) is PF-06741086.

Study Treatment	Route of Administration	Protocol Term
PF-06741086, Solution for Injection, 150 mg/mL	subcutaneous (SC)	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 (interactive Web-based response [IWR]). 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, and the subject number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

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 will be permitted to self-administer PF-0674106 once they have demonstrated an understanding of the preparation and administration process at the site. Confirmation of a subject's ability to perform preparation and administration must be documented in the site file. For self-administration of PF-06741086 at home, compliance will be captured and completed by the subject by completing the subject diary.

Subjects will self-administer treatment weekly from the point of which they have demonstrated the capability to do so (as stated above) until Day 365 (see Section 3.2). Prior to self-administration, sites must ensure subjects are trained on IP administration and storage per the IP manual. Dosing between planned clinic visits may be administered by investigational site staff until the respective subject has been properly trained in self-administration. Sites should follow-up (eg, via phone call) to ensure compliance with administration instructions, where necessary. Day 337 (Month 12) will be the final visit where IP is dispensed for self-administration. For subjects being treated in the clinic, 7 days before Day 365 is the final date that IP is administered in the clinic.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

PF-06741086 Solution for Injection (150 mg/mL) 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

The investigational product will be dispensed using an IRT drug management system at each visit from Day 1 to Day 337. A qualified staff member will dispense the investigational product via unique container numbers in the cartons provided, and in quantities appropriate so that subjects self-administering treatments at home will receive enough investigational product to cover the number of doses until the next scheduled clinic visit. The subject/caregiver should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the investigational product is to be administered.

See the Investigational Product Manual (IPM) for instructions on how to prepare the investigational product for administration. Investigational product should be prepared, when necessary, and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. These requirements will not apply for self-administration by subjects.

5.4. Administration

Investigator site personnel, the subject and/or the subject's caregiver will administer investigational product according to the subject diary. Site personnel will instruct the subject or designated person on the proper sterile technique to prepare and administer a SC injection at home. During the Day 1 visit, the initial dose of investigational product must be administered in the office by study personnel, while the subject and/or the subject's caregiver observes.

For all SC treatments, 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. Other locations (eg, abdomen) are acceptable if required. CCI [redacted] Multiple injections should use a unique site for each injection where possible, to limit the injection site volume to 1 mL (ie, 1 mL in arm, 1 mL in thigh for a 2 mL, 2 injection dose). When feasible, if multiple injections are required, the simultaneous use of both arms (eg, 1 mL in left arm and 1 mL in right arm) should be avoided.

All self-administration information will be documented in the subject diary.

5.5. Investigational Product Storage

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

Investigational products should be stored in their original containers and in accordance with the labels.

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

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 they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information that the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the storage requirements for take home medications, including how to report temperature excursions.

5.6. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All unused study drug must be returned to the investigator by the subject at every visit and at the end of the trial.

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 investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

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

Routine prophylaxis with FVIII or FIX replacement therapy, or bypass agent therapy (rFVIIa, APCC or emicizumab), is prohibited throughout the study for all subjects.

FVIII (within 72 hours) or FIX replacement therapy (within 96 hours), or bypass agent therapy (rFVIIa or APCC: within 72 hours; for other products: 5 half-lives) 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 FVIII or FIX 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.

FVIII (within 72 hours) or FIX replacement therapy (within 96 hours), or bypass agent therapy (for rFVIIa or APCC: at least 72 hours; for other products: 5 half-lives), 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.

Subjects who received treatment with extended half-life (EHL) FVIII or FIX products may require longer washout periods than those noted above; careful consideration by investigators should be given to the dose and half-life of these treatments prior to planning the duration of washout.

Treatment with rFVIIa **at a dose level greater than approximately 90 µg/kg, or administered at intervals more frequent than every 2 hours, is prohibited throughout the study.** If a subject receiving investigational product is subsequently administered a rFVIIa dose greater than approximately 90 µg/kg, or requires dosing more frequently than every 2 hours 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 activated prothrombin complex concentrate (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 393 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 365 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 FVIII or FIX 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

All subjects participating in this study must sign the B7841003 informed consent or assent document (and parental consent must be completed, where required). The investigator (or an appropriate delegate at the investigator site) will obtain informed consent or assent from each subject in accordance with the procedures described in the Subject Information and Consent section (Section 12.3).

For subjects who completed study B7841002 within 30 days of the Day 1 visit of study B7841003, informed consent procedures will occur at the Day 1 visit. Screening activities for these subjects, following informed consent, will consist of using results from the final visit of study B7841002 to confirm that none of the B7841003 study exclusion criteria (Section 4.2) have been met.

Medical history data for subjects from study B7841002 will also be used for subjects enrolling into B7841003. Resolved AEs from B7841002 may be entered as additional medical history, where applicable.

For subjects who have completed participation in study B7841002 more than 30 days prior to the Day 1 visit in study B7841003, and for subjects enrolled de novo into study B7841003, the following screening activities will apply:

The following procedures will be completed during Screening:

- Obtain written informed consent.
- Review Inclusion and Exclusion criteria.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken since the start of Screening.
- 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.
- CCI [redacted]
- Following at least a 4-hour fast collect blood and urine specimens for the following for shipment to the study central laboratory:
  - Urinalysis;
  - Serum chemistry;
  - Hematology.

The following additional screening procedures apply to de novo subjects who did not participate in study B7841002.

- For adolescent subjects, obtain assent (and parental consent, where required).
- Collect demography, height and weight.
- Obtain medical history, including hemophilia history and inhibitor history, and collect the number of bleeding episodes over the past 6 months.
- Review use of FVIII or FIX replacement therapy, or bypass agent therapy, to ensure subject meets washout criteria prior to Screening.
- 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:
    - FVIII and FIX activity;
    - CD4 cell count;
    - Prothrombin 20210 mutation testing;
    - Factor V Leiden mutation testing;
    - Lipid panel;
    - Protein C activity/Protein S level;
    - Fibrinogen;
    - Serology (HBs Ag, HBc Ab, HCV Ab, and HIV).
- Collect single 12-lead electrocardiogram (ECG). If ECG is abnormal, collect triplicate ECG.

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 [redacted] samples:

- Prothrombin 20210 mutation testing.
- Factor V Leiden mutation testing.
- [redacted]
- FVIII and FIX activity.

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Requirements 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.

- Blood pressure/pulse rate: prior to blood specimen collection.
- [redacted]
- Other procedures (eg, training subject on self-administration, diary compliance).

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 [+1 day]

The Day 1 visit for B7841003 may occur on the same day (same visit to the clinic) as the B7841002 Day 85 or Day 113 visit. All Day 1 (or B7841002 Day 85 or Day 113) blood draws must be done prior to administration of IP.

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

- **For subjects who completed study B7841002, obtain written informed consent.**
- Assess baseline symptoms/AEs.
- Review changes in subject's concomitant treatment information.
- Review use of FVIII or FIX replacement therapy, or bypass agent therapy, to ensure any de novo subject meets washout criteria prior to **Day 1**.

- Review changes in the subject's medical history including medication.
- Collect information on new bleeding episodes.
- Review Inclusion and Exclusion criteria for any de novo subject.
- Conduct a limited physical examination at the discretion of the investigator, if clinically indicated, to assess changes of any ongoing symptoms.
- Confirm proper contraception is being used.
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure.
- Collect blood and urine specimens for the following for shipment to the study central laboratory:
  - Urinalysis;
  - Serum chemistry;
  - Hematology with differential panel;
  - FVIII and FIX activity;
  - [redacted]
  - PT;
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- For de novo subjects, the following activities are also required prior to dosing:
  - Collect blood and urine specimens for the following for shipment to the study central laboratory:
    - Fibrinogen;

- Cardiac troponin I.

- Collect triplicate 12-lead ECG.

- 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:

- 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 [±1 day], Day 4 [±1 day], Day 8 [±2 days], Day 15 [±2 days], Day 22 [±2 days] and Day 29 [±2 days] – CCI Treatment Visits for De Novo Subjects

The following procedures will be completed at the visits above for de novo subjects **only**:

- 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 blood specimens for the following for shipment to the study central laboratory (note that Day 29 blood specimens are in addition to Day 29 activities performed on all study subjects per Section 6.2.3):

  CCI [redacted]

  - Serum chemistry (Day 8, 15, 22, 29);

  - Hematology with differential panel (Day 8, 15, 22, 29);

- [redacted]
- PT (Day 8, 15, 22, 29);
- [redacted]
- [redacted]
- [redacted]
- Cardiac troponin I (Day 8, 15, 22, 29).

- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure. (Day 29).
- Collect single 12-lead ECG. If ECG is abnormal, collect triplicate ECG (Day 29).
- **Day 8, Day 15 and Day 22** - After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections).
  - Monitor injection site reactions.
  - Collect the subject's diary and review with the subject/caregiver, including information about study compliance, investigational product infusions, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary.

6.2.3. Day 29 [±2 days], Day 57 [±5 days], Day 85 [±5 days], Day 113 [±7 days], Day 141 [±7 days], Day 169 [±7 days], Day 225 [±7 days], Day 253 [±7 days], Day 281 [±7 days], Day 309 [±7 days], Day 337 [±7 days], and Day 365 [±7 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.
- Confirm proper contraception is being used.
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure.

- Collect blood specimens for the following for shipment to the study central laboratory.
  - **De novo subjects only**:
    - Serum chemistry (Day 57);
    - Hematology (Day 57).
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, investigational product infusions, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions. Dispense new subject diary.
- Monitor infusion/injection site reactions.
- **Day 85 [±7 days], Day 169 [±7 days], Day 253 [±7 days], and Day 365 [±7 days]** - Collect blood and urine specimens for the following for shipment to the study central laboratory:
  - Urinalysis;
  - Serum chemistry;
  - Hematology with differential panel;
  - FVIII and FIX activity;
  - [redacted]
  - PT;
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- After all pre-dose procedures have been completed, administer the investigational product (see STUDY TREATMENTS and Administration Sections).
- Dispense investigational product to self-administration at home (if applicable).
  - **Day 337** is the final visit for dispensing investigational product to the subject for self-administration.

- No IP will be administered or dispensed on **Day 365**.

6.2.4. Day 393 [±7 days] – End of Study 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 full physical examination.
- Collect the subject's diary and review with the subject/caregiver, including information about study compliance, investigational product infusions, bleeding assessments (including site and traumatic/spontaneous) and injection site reactions.
- Confirm proper contraception is being used.
- Collect weight.
- Obtain pulse rate, respiratory rate, oral temperature, and supine blood pressure.

6.2.5. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject may be done via a phone call.

6.3. Subject Withdrawal or Early Termination

Withdrawal of consent:

Subjects who request to discontinue receipt of 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 her 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. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

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 locally permissible 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 (see also the Withdrawal From the Study Due to Adverse Events section) 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. 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, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

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.

Subjects who withdraw from the study for reasons other than safety may be replaced at the discretion of the sponsor.

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 manner.

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

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the Schedule of Activities 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 3. Laboratory Tests

Hematology[d]	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 CCI [redacted] Fibrinogen Cardiac Troponin I (for de novo subjects only) Factor VIII[c] Factor IX[c] Factor VIII and Factor IX inhibitor[e] 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. For de novo subjects at Screening only.
c. For de novo subjects at At Screening and Day 1 only.
d. Differential hematology panel required at Days 1, 85, 169, 253 and 365.
e. 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. 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.

CCI [redacted]

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. 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 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 coagulation factor products). 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 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 8.2.3 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 coagulation factor products or rFVIIa bypass agent therapy at approximately 90 µg/kg, administered at intervals ≥2 hours) 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.

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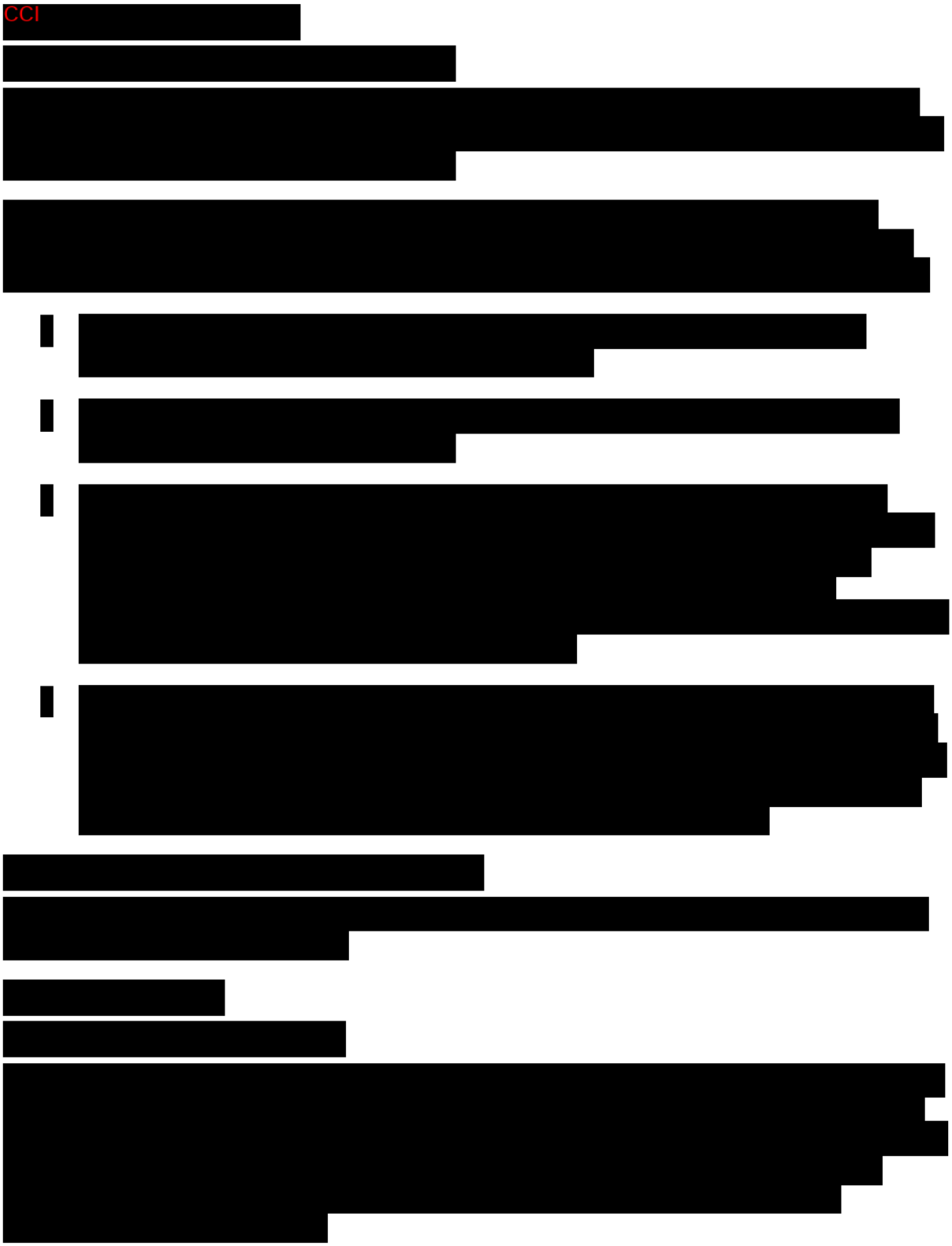

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7.8. Blood Volume

The total blood sampling volume for de novo subjects in this study is a maximum of approximately 254 mL (based on Screening through Day 197). Subjects continuing from B7841002 will have an approximate maximum of 125 mL drawn during the study. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the approximate 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 4. Blood Volume

Sample Type	Sample Volume (mL)	Number of Sampling Times[c]			Total Volume (mL)
		Screening	Study Period	Follow-Up	
Safety Labs					
Serum chemistry (with Lipid profile[a])	5	1	7	0	45
Hematology[d]	3	1	7	0	27
Prothrombin 20210 mutation	3	1	0	0	3
Factor V Leiden mutation testing	3.5	1	0	0	3.5
PT/INR, Factor VIII and Factor IX activity,[b] Fibrinogen, Protein C,[a] Protein S,[a] CCI [Single combined sample]	4.5	1	9	0	49.5
Factor VIII and Factor IX inhibitor[a]	4.5	1	0	0	4.5
CD4 cell count absolute (CD4)[a]	5	1	0	0	5
Serology (HBs Ag, HBc Ab, HCV Ab, and HIV)	5	1	0	0	5
Cardiac Troponin I[e]	3		5		15
CCI					

[a] de novo subjects at Screening only.
[b] de novo subjects at Screening and Day 1 only.
[c] total samples reflects amount required for de novo subjects (with Screening and additional visits during first month of treatment); subjects continuing from B7841002 will have less samples drawn and thus less maximum blood volume.
[d] screening specimen only for novo subjects and for subjects enrolling >30 days following day 85 or day 113 visit in study B7841002,
[e] at days 1, 8, 15,22 and 29 for de novo subjects only.

Table 5. 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.
CCI [redacted]	[redacted]

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious 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.

As noted in the Protocol-Specified Serious Adverse Events section, should an investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product, the investigator must report the SAE to Pfizer Safety within 24 hours of investigator awareness.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF 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 the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal or Early Termination section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. 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.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;

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

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 (outside of any protocol-specified dose adjustments) 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 recording as an AE.

8.2.3. 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 8.2.4). 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.

8.2.4. 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.

Or that is considered to be:

- An important medical event.

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.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items:

  - Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization.

- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;

- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.5. 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 is 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 a 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 SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or Life threatening to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Corresponding numerical toxicity grade	Severity	
1	MILD	Does not interfere with subject's usual function.
2	MODERATE	Interferes to some extent with subject's usual function.
3	SEVERE	Interferes significantly with subject's usual function.
4	Life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care required.

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.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

Thromboembolic or ischemic events are considered important medical events. As important medical events, Pfizer is to be notified within 24 hours of awareness of any thromboembolic or ischemic event. Data entry and additional reporting requirements will follow the same instructions for all other SAEs as listed in Section 8.1.

8.4.2. Potential Cases of Drug-Induced Liver Injury

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

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

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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

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

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

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.3.1. Exposure During Pregnancy

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

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

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

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. Occupational Exposure

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

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

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

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

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

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

In the event of a medication dosing error, the sponsor should be notified immediately.

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

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

8.5. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be recorded on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might lead to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

No formal statistical hypothesis will be tested. The total sample size of approximately 36 subjects (24 subjects from B7841002 and 12 additional de novo subjects) is based on the number of subjects enrolled in study B7841002, and on clinical considerations to balance the need to minimize exposure of study subjects to the test article with the need to provide adequate safety and tolerability data for clinical development.

9.2. Efficacy Analysis

9.2.1. Analysis of the Efficacy Endpoint

ABR will be calculated and summarized descriptively. The ABR is calculated as (number of bleeding events/observed treatment period in days)*365.25.

CCI [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 treatment-emergent AEs (TEAEs), withdrawals due to TEAEs, and infusion and injection site reactions will be summarized by dose level. Abnormal safety findings will also be presented separately for inhibitor subjects 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. CCI [redacted]

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.

9.7. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, CCI and/or to support clinical development.

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 investigator site may be subject to review by the IRB/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 investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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. 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 the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator 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 and any subject recruitment materials 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 and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her 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.

Where required, provisions for post-trial investigational product availability will be made in accordance with local CA/EC rules and regulations.

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study 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, 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 (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final 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 PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (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 the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 investigator sites, and that any subsequent publications by the PI 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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5. Dahm A, Vlieg AVH, Bendz B et al. Low levels of tissue factor pathway inhibitor (TFPI) increase the risk of venous thrombosis. *Blood.* 2003;101:4387-4392.

Appendix 1. Abbreviations

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

Abbreviation	Term
ABR	annualized bleeding rate
CCI	[redacted]
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
AUC	area under the curve
CCI	[redacted]
BID	bis in die ("twice a day')
BMI	body mass index
BP	blood pressure
CD4	CD4 count absolute
CDC	complement dependent cytotoxicity
CK	creatine kinase
Cmax	maximum concentration
CNS	central nervous system
CRF	case report form
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CTA	clinical trial application
CV	cardiovascular
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
dPT	dilute Prothrombin Time
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EHL	extended half-life
EU	European Union
EudraCT	European Clinical Trials Database
FcR	Fc (fragment crystallizable) receptor
FEIBA	Anti-inhibitor Coagulant Complex (proprietary name)]

Abbreviation	Term
FIB	fibrinogen
FIH	first-in-human
FSH	follicle-stimulating hormone
FVIIa	activated coagulation factor VII
FVIII	factor VIII
FIX	factor IX
FXa	factor Xa
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
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 virus antibody
HIV	human immunodeficiency virus
HRQL	health-related quality of life
ICH	International Conference on Harmonisation
ID	identification
IgG	immunoglobulin G
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
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LFT	liver function test
LLN	lower limit of normal
LSLV	last subject last visit
MAD	multiple ascending dose
N/A	not applicable
CCI	[redacted]
NOAEL	no observed adverse effect limit
PCD	primary completion date
PD	Pharmacodynamics(s)
PFS	prefilled syringe
CCI	[redacted]

Abbreviation	Term
CCI	[redacted]
PE	physical exam
PI	principal investigator
PK	pharmacokinetic
PT	prothrombin time
QM	quaque monthly ("once monthly")
QW	quaque weekly ("once weekly")
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	standard operating procedure
SPR	surface plasmon resonance
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
Tbili	total bilirubin
TEG	thromboelastography
TFPI	tissue factor pathway inhibitor
TGA	thrombin generation assay
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States

Appendix 2. 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	