CLINICAL PROTOCOL

A PHASE 1B MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND TOLERABILITY AND DETERMINE THE MAXIMUM TOLERATED DOSE OF PF-05230907 IN SUBJECTS WITH INTRACEREBRAL HEMORRHAGE (ICH)

Compound:	PF-05230907
Compound Name:	Factor Xa Variant (I16L)
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2015-005703-83
Protocol Number:	B2341002
Phase:	1b

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale

Amendment 2	17 JAN 2017	• Protocol Summary:
		  • Removed the requirement for AEs to be in the same system organ class from the criteria for sequential dosing and ad hoc eDMC meetings. This was required by regulatory authorities in Germany.
		• Schedule of Activities:
		  • Added requirement for Sponsor and investigator documentation of TIEs on Day 8 to footnote 'm'.
		  • Added footnote 's' to indicate the requirement for safety labs to be analyzed locally along with central lab analysis for sites in Germany. This was required by regulatory authorities in Germany.
		  • Added foot note 't' to include cardiac troponin T samples for local analysis only.
		• Section 3.1. Sequential Dosing:
		  • Removed the requirement for AEs to be in the same system organ class from the criteria for sequential dosing.
		  • Added cardiac troponin T results to the requirements for 72-hour safety data review. This applies only to sites where cardiac troponin T is analyzed locally.
		• Section 3.3. eDMC Review of Cohort Safety Data:
		  • Removed the requirement for AEs to be in the same system organ class from the criteria for ad hoc eDMC meetings.
		• Section 4.1. Inclusion Criteria:
		  • An additional requirement for informed consent (referenced in Appendix 8) was added for subjects in Sweden. This requirement was requested by regulatory authorities in Sweden.

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		• Section 4.6.2.2 Glasgow Coma Scale:
		  • Removed the requirement for certification documentation and/or sponsor training. GCS is a standard clinical assessment which does not require specific training.
		• Section 6.2.2. Day 1 Hour 0 Minute 5:
		  • For sites in Germany, the requirement for safety labs to be analyzed locally along with central lab analysis was added.
		• Section 6.2.3. Day 1 Hour 0 Minute 45:
		  • For sites in Germany, the requirement for safety labs to be analyzed locally along with central lab analysis was added.
		• Section 6.2.4. Day 1 Hour 3:
		  • Cardiac troponin T, where applicable, was included for sample collection.
		• Section 6.2.5. Day 1 Hour 9:
		  • Cardiac troponin T, where applicable, was included for sample collection.
		• Section 6.2.6. Day 2 (24 Hours):
		  • For sites in Germany, the requirement for safety labs to be analyzed locally along with central lab analysis was added.
		  • Cardiac troponin T, where applicable, was included for sample collection.
		• Section 6.2.7. Day 3 (48 Hours):
		  • Cardiac troponin T, where applicable, was included for sample collection.
		• Section 6.2.8. Day 4 (72 Hours):
		  • For sites in Germany, the requirement for safety labs to be analyzed locally along with central lab analysis was added.

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		• Cardiac troponin T, where applicable, was included for sample collection. • Section 7.1.6. Cardiac Troponin I: • A statement on the precedence of centrally-analyzed troponin I, versus locally analyzed troponin T, for safety data review purposes was added. • Section 7.1.9 Clinical Laboratory Tests: • For sites in Germany, the requirement for safety labs to be analyzed locally along with central lab analysis was added. • Section 9.8 Data Monitoring Committee: • Removed the requirement for AEs to be in the same system organ class from the criteria for ad hoc eDMC meetings. • Section 13. Definition of End of Trial: • Section 13 was revised to define the end of the trial as last subject last visit (LSLV) for all participating countries. Previous version had a separate definition for EU Member States. This change was required by regulatory authorities in Sweden. • Appendix 8 Definition for Subjects Capable of Providing Consent in Sweden: • Appendix 8 was added to the protocol to provide the definition for subjects capable of providing consent in Sweden. This was a requirement from regulatory authorities in Sweden.
Amendment 1	27 JUN 2016	• Protocol Summary: • "Changes in Factor V after dosing with PF-05230907" was incorrectly listed as an exploratory endpoint in this study and was removed. • A paragraph summarizing additional safeguards for subject safety requested by regulatory

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		agencies was added, including rules for sequential dosing, rules for dose pausing, eDMC dose escalation oversight, and additional eDMC safety review. • The criteria for a pause in dosing pending eDMC review of adverse event data were added. • The requirement for an interim review memo from the eDMC chair that authorizes dose escalation was added. • eDMC recommendations were added as an input for limiting dose escalation increments. • The incorrect visit day (Day 8) was referenced for observing treatment emergent modulations of laboratory safety biomarkers. The correct visit day - Day 4 – was added. • The maximum sample size was changed from 50 to 51, to correctly reflect the maximum sample size enrolled in this study under mCRM restrictions. • Schedule of Activities: • Blood sample for Factor V activity at Screening was removed as this parameter will no longer be evaluated in this study. • Table and footnote [h] were updated to include the collection of baseline height data, which may be subject reported. This requirement was not specified in the previous text. • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis. • Missing text Doppler ultrasonography was added to footnote [e]. • Section 1.5. Dose Rationale: • Sequential dosing was added as mitigation against the unanticipated risks of exposure at higher doses.

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		• eDMC recommendations were added as an input for limiting dose escalation increments. • Section 3. Study Design: • A paragraph summarizing additional safeguards for subject safety requested by regulatory agencies was added, including rules for sequential dosing, rules for dose pausing, eDMC dose escalation oversight, and additional eDMC safety review. • Section 3.1. Sequential Dosing: • 3.1 added as a new section to describe rules governing sequential dosing. • The requirements and criteria for sequential dosing of cohorts (at dose levels not previously administered) were added. • Brain imaging for 72 hour safety review was revised to correctly reflect the use of both CT and MRI. • Cardiac troponin I was added as a parameter for 72 hour safety review. • The criteria for a pause in dosing pending eDMC review of adverse event data were added. • Section 3.2. Progression to Subsequent Cohort: • 3.2 added as a new section to describe rules governing progression to the next cohort and dose escalation. • eDMC recommendations were added as an input for dose level assignments. • Section 3.3. eDMC Review of Cohort Safety Data: • 3.3 added as a new section to describe eDMC review of safety data and eDMC chairperson authorization for dose escalation. • The requirement for an interim review memo from the eDMC chair that authorizes dose escalation was added.

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		• The criteria for a pause in dosing pending eDMC review of adverse event data were added. • Section 3.4. Stopping Rules for mCRM Algorithm: • 3.4 added as a new section to describe the stopping rules for dose level assignment by the mCRM algorithm. • The maximum sample size was changed from 50 to 51, to correctly reflect the maximum sample size enrolled in this study under mCRM restrictions. • Table 2 – Dose Escalation Schema was moved to this section. • Figure 1 – CRM Process Flow Schematic was moved to this section and updated to include sequential dosing process steps. • Section 3.5. Duration of Study Participation: • 3.5 added as a new section to describe length of study participation per subject. No changes were made to the text in this section. • Section 4.1. Inclusion Criteria: • Inclusion criterion #1 was modified to include a clause stating that legal representatives may only consent subjects in countries where this is accepted. • Section 4.6.2.1. Modified Rankin Score mRS: • The requirement for site source documentation was added. • Section 5.3.1. Dosage Form(s) and Packaging: • IP descriptions were updated, and reconstitution volume with NaCl concentration was added for administrative purposes. • Section 5.3.2. Preparation and Dispensing: • IP description was removed, with text added for administrative purposes.

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		• Section 5.5. Investigational Product Storage:
		  • IP description was removed for administrative purposes.
		• Section 5.7.2. Prohibited During the Study:
		  • Low dose subcutaneous low-molecular weight heparin and unfractionated heparin were added as acceptable treatments in accordance with published guidelines for the treatment of stroke.
		• Section 6.1. Screening:
		  • The collection of baseline height data was added, which may be subject reported. This requirement was not specified in the previous text.
		  • Blood sample for Factor V was removed as this parameter will no longer be evaluated in this study.
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.
		• Section 6.2.3. Day 1 Hour 0:
		  • The PD sample for Factor V was removed as this parameter will not be evaluated in this study.
		• Section 6.2.4. Day 1 Hour 3:
		  • The requirement for obtaining an actual weight as soon as possible post-dose was added to conform with the requirement listed in the Schedule of Activities (footnote h).
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.
		• Section 6.2.5. Day 1 Hour 9:
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.

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		• Section 6.2.6. Day 2:
		  • Blood sample for Factor V was removed as this parameter will no longer be evaluated in this study.
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.
		• Section 6.2.7. Day 3:
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.
		• Section 6.2.8. Day 4:
		  • A blood sample for ADA, NAb, and Factor X activity must be collected if the subject is discharged at Day 4. The previous text did not include this.
		  • Cardiac troponin I labs were updated to allow either local laboratory analysis or central laboratory analysis.
		• Section 6.2.9. Day 8 or Discharge:
		  • A blood sample for Factor X activity must be collected at this visit. The previous text did not include this.
		• Section 8.6.1. Protocol Specified Serious Adverse Events:
		  • Peripheral arterial ischemia was added to the list comply with Appendix 1.
		• Section 9.1. Statistical Methods:
		  • The maximum sample size was changed from 50 to 51, to correctly reflect the maximum sample size enrolled in this study under mCRM restrictions.
		• Section 9.3. Sample Size Determination:
		  • The maximum sample size was changed from 50 to 51, to correctly reflect the maximum sample size enrolled in this study under mCRM restrictions.

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		• Section 9.8. Data Monitoring Committee:
		  • The criteria for a pause in dosing pending eDMC review of adverse event data were added.
		  • The requirement for an interim review memo from the eDMC chair that authorizes dose escalation was added.
		• Section 12.1. Institutional Review Board /Ethics Committee:
		  • It should be noted that for substantial amendments to the protocol, national competent authority approval is also required prior to implementing the amendment. The previous text did not include this.
		• Section 12.2. Ethical Conduct of the Study:
		  • The protocol will be conducted in accordance with the current version of the Declaration of Helsinki. The protocol incorrectly referenced the 2008 version; this year was removed from the text to comply with regulatory requests.
		• References:
		  • A reference for the NIH Stroke Scale contained a link to the National Institute of Neurological Disorders and Stroke webpage that is no longer associated with the NIHSS. The following correct link was added.
		http://www.ninds.nih.gov/disorders/stroke/strokescales.htm

Original protocol	17 December 2015	Not applicable (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

Background and Rationale:

Spontaneous intracerebral hemorrhage (ICH) is a major cause of death and disability accounting for approximately 10-15% of stroke cases worldwide. ICH continues to be associated with poor clinical outcomes, approximately 35-52% of patients die within one month, mortality at 6 months ranges from 23-58% and a large number of individuals fail to regain functional independence by six months. The current management of ICH is largely supportive and the lack of effective treatment for ICH remains a critical and unmet need.

FXa occupies a central position in the coagulation cascade between thrombin-generation and the intrinsic (Factor VIII/Factor IX dependent) and extrinsic (Factor VII/Tissue Factor dependent) pathways. Membrane-bound FXa, in the presence of its cofactor Factor Va (FVa), converts prothrombin to thrombin, which activates platelets and converts fibrinogen to fibrin to form a thrombus. FXa is the only activator of prothrombin. Pfizer and its collaborators have identified a novel variant of coagulation FXa (PF-05230907) that may establish, without excessive thrombotic risk, localized hemostasis at the site of bleeding in a number of clinical situations of uncontrolled bleeding such as ICH. Given the severe morbidity and mortality associated with ICH and given the need to better define the maximum tolerated dose (MTD) of PF-05230907 in order to plan future efficacy studies, a modified continual reassessment method (mCRM) will be implemented to determine the MTD based on frequency of treatment emergent thromboembolic and/or ischemic events (TIEs). A target TIE rate of 15% represents approximately a 5-10% increment above the background rate and is considered compatible with acceptable benefit risk in the high morbidity, high mortality indication of ICH.

Objectives and Endpoints:

Primary Objective:

- Based on the mCRM algorithm, determine the maximum tolerated dose (MTD) of PF-05230907 administered once as an intravenous (IV) bolus in subjects with ICH.
- Determine the overall safety and tolerability of PF-05230907.

Secondary Objectives:

- Evaluate pharmacodynamic (PD) effects of treatment with PF-05230907.
- Determine the frequency of antibody immune response to PF-05230907.

Exploratory Objectives:

- Assess hemostatic efficacy of PF-05230907.
- Characterize the pharmacokinetic (PK) profile of PF-05230907.
- Assess effect of PF-05230907 on exploratory markers of PD in subjects with ICH.

- Assess potential measures of neuro-inflammation and/or neurologic outcomes in subjects with ICH.
- Assess brain imaging parameters that may be associated with efficacy or safety of treatment with PF-05230907 and/or outcomes in ICH.
- Determine frequency of antibody immune response against proteins from host cells used in manufacture of PF-05230907.
- Assess neurological outcome measures.
- Assess health resource utilization.

Primary Endpoint:

- Frequency of treatment emergent thromboembolic and/or ischemic events (TIEs) in subjects treated with PF-05230907 through Day 8.
- Treatment emergent serious adverse events as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 43.
- Treatment emergent adverse events as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 8.
- Treatment emergent laboratory abnormalities as characterized by type, frequency, and severity through Day 4 (or discharge).
- Physical examination changes through Day 8 (or discharge).
- Vital sign changes through Day 8 (or discharge).
- Electrocardiogram (ECG) results through Day 8 (or discharge).

Secondary Endpoints:

- Changes in activated partial thromboplastin time (aPTT) and prothrombin fragment 1+2 (PF1+2) after dosing with PF-05230907 through Day 2.
- Anti-drug antibody/neutralizing antibody (ADA/NAb) and Factor X activity through Day 43 and/or Day 91 follow-up visit.

Exploratory Endpoints:

- ICH absolute and percent change from baseline volume at 24 hours (see Schedule of Activities [SOA]).
- PF-05230907 concentration in plasma.

- Changes in other exploratory biomarkers that may reflect pharmacologic effect of PF-05230907 or ICH progression may be evaluated.
- Potential biomarkers of neuro-inflammation and/or neurological outcomes to better understand ICH and/or its outcomes.
- Computed tomography (CT) parameters that may inform future investigations of PF-05230907 and/or the condition of ICH.
- Anti-Chinese hamster ovary (CHO) protein antibodies.
- Anti-paired basic amino acid cleaving enzyme (PACE) furin antibodies.
- Neurologic function as assessed by the NIHSS.
- Surrogate measures for health resource utilization, may include duration of stay in stroke/intensive care unit (ICU), duration of hospital stay, duration of inpatient rehabilitation, and duration of outpatient rehabilitation.

Study Design:

This study employs a modified continual reassessment method (mCRM) design to estimate the MTD, defined as a target toxicity rate of 15% based on the treatment emergent thromboembolic and/or ischemic events (TIEs). The mCRM design utilizes Bayesian methodology to continuously learn the dose-toxicity relationship, which is characterized by a parametric model. The details of this design are described in the statistical method section of this protocol.

Subjects will be enrolled in cohorts, starting with an initial dose of 5 μg/kg for the first cohort (the highest dose safely administered in the first in human clinical study [B2341001]). As safeguards for subject safety, (a) dose escalation will be conducted in a limited number of subjects per cohort (N=3), (b) sequential dosing of study subjects will be implemented in each cohort evaluating a dose level that exceeds previously administered dose levels and rules will apply governing additional cohorts at the respective dose level that are subject to sequential dosing, (c) dosing will be paused following completion of each cohort until safety is assessed for the respective cohort (d) safety laboratory biomarker criteria are implemented which trigger smaller maximum increments for dose escalation, (e) enrollment of the next cohort will not proceed until a safety review has been completed for the preceding cohort and the chair of the external Data Monitoring Committee (eDMC) has provided authorization and (f) criteria are implemented which trigger an automatic eDMC review of safety at a respective dose level,

Severity of adverse events (AEs) and serious adverse events (SAEs) will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. TIEs will be defined as any of the listed events at the respective severity grade indicated in Appendix 1. All subjects who receive PF-05230907 are evaluable for TIEs. The determination of MTD using mCRM modeling will be based on TIEs which occur through 7 days post-dose (Day 8).

The total length of time planned for study participation is approximately 3 months; 6.0 hours for screening, a single dose administration with a 4 day minimum hospital confinement period and follow-up visits through Day 91.

The range of doses that may be explored will be from a grid of doses ranging from 1 μg/kg to 47 μg/kg. If the modeled rate of TIEs at the 5 μg/kg starting dose exceeds the pre-specified target toxicity rate of 15% for the MTD, lower doses may be explored. Starting with the second cohort, subjects will be assigned to a dose in the predefined dose grid that is closest to, but not exceeding, the currently predicted MTD based on a parametric dose-toxicity model that the mCRM utilizes to learn about the overall dose-TIE relationship subject to additional dose escalation constraints and clinical oversights. The dose-toxicity model is updated based on the frequency of TIEs in each completed cohort. Under the adopted mCRM design, the dose level for each subsequent cohort can be escalated, deescalated, or restudied but always aiming towards the MTD target for frequency of TIEs. However, dose level assignments may be modified to more conservative dose levels based upon sponsor medical judgment or eDMC recommendations. To prevent overly aggressive dose-escalation, the maximum allowed dose increase from the highest dose that has been previously studied is limited to 2 increments at a time (ie, not more than one dose level may be skipped) which results in 50-67% increase in dose for the 5 μg/kg dose and above. If treatment emergent modulation of one or more of the following laboratory safety biomarkers is observed during the interval from baseline to Day 4 (or discharge), as indicated below, dose increase will be limited to only 1 increment at a time (ie, no more dose skipping):

- Fibrinogen:
    - If baseline value is within normal reference range: a post-dose value ≤50% of the lower limit of normal.
    - If baseline value < lower limit of normal reference range: a post-dose value ≤50% of the baseline value.
- Platelet Count:
    - If baseline value is within normal reference range: a post-dose value of <100,000.
    - If baseline value < lower limit of normal reference range: a post-dose value ≤50% of the baseline value.
- PT: a post-dose value that is prolonged by >4 seconds above the baseline value.

If a Suspected Unexpected Serious Adverse Reaction (SUSAR) or 2 or more grade 3 or higher adverse events that are considered at least possibly related to treatment with PF-05230907 are observed in the initial cohort evaluating a dose level that exceeds previously investigated dose levels, then the subsequent (second) cohort evaluating the respective dose level will also be subject to sequential dosing restrictions. If either of these criteria are met, then dosing at the respective dose level (and at higher dose levels) will be paused until a meeting of the eDMC has been convened.

In addition to TIEs and available safety biomarker data, other available safety data (including clinically significant AEs or SAEs) will also be assessed. These events will not have any impact on mCRM-determined dose recommendations but may be used to inform dose assignments more conservative than those derived by the mCRM dose-toxicity model. An enrollment pause will occur after each respective cohort completes dosing until the following are completed: sponsor review of the available safety data through Day 8 (or discharge) post-dose administration, discussion with the investigator(s)/sub-investigator(s) for each subject in the respective cohort, submission of an interim review memo including all 7-day safety data to the eDMC chair (or designee), authorization to proceed with enrollment from the eDMC chair (or designee), mCRM-determined dose recommendation, and adjustment of mCRM-determined dose to more conservative dose levels when deemed appropriate by the sponsor or eDMC.

Study Treatment:

The investigational product should be prepared and dispensed by appropriately qualified and trained site personnel (eg, pharmacist, pharmacy technician, study nurse) designated to participate in the study as permitted by local, state, and institutional guidance. PF-05230907 will be reconstituted as outlined in the Investigational Product Manual. Depending on the total dose required for a subject, one Placebo for PF-05230907 (diluent) vial may be required for dilution of the investigational product to prepare an appropriate concentration of the final dosing solution. The appropriate dose will be drawn up into an individual dosing syringe for administration. Investigator site personnel will administer investigational product as a single IV bolus on Day 1.

Statistical Methods:

This study employs a modified (mCRM) design similar to Goodman et al. to estimate the MTD. The mCRM design utilizes Bayesian methodology to learn the dose-toxicity relationship continuously after each cohort's thromboembolic and/or ischemic event (TIE) data becomes available. The underlying dose-TIE relationship is assumed to follow a one-parameter hyperbolic-tangent model.

$$f(x, \beta) = [\frac{1 + \tanh(x)}{2}]^{\beta},$$

where β is an unknown parameter with a prior distribution pre-specified at the beginning of the trial, x an adjusted dose which is computed from an initial (β =1) dose-toxicity curve projected based on clinical input, and tanh is the hyperbolic-tangent function.

Once all the TIE data become available from the current cohort, the posterior distribution of β will be generated through the Markov Chain Monte Carlo (MCMC) simulations in adaptive design explorer (ADE). The model-based MTD will be estimated as $f^{-1}(0.15, \hat{\beta})$, where 0.15 is the pre-specified target TIE rate at MTD and $\hat{\beta}$ is the posterior mean of β. The next cohort of 3 subjects will be dosed at the dose level closest to this estimated MTD but not exceeding it, subject to additional pre-specified dose escalation constraints and clinical

oversight. The posterior distribution of β will become the prior distribution in the next round of updates. This process is continued until at least one of the following stopping rules is met:

1. Maximum sample size of 51 subjects has been reached.

2. MTD has been identified with sufficient accuracy, ie, 12 subjects have been accumulated on a dose that is currently estimated to be the MTD.

3. All doses appear to be overly toxic and MTD cannot be determined in the current trial setting.

Starting from the second cohort and until the end of the trial, the above described mCRM algorithm constantly incorporates additional information about dose-TIE relationship learned from the data via modeling and that is reflected on the projected MTD. By design, such dose allocation procedure will eventually cluster dose assignments around the dose yielding an approximate 15% TIE rate.

Pharmacokinetics Analysis

PF-05230907 concentration in plasma is an exploratory endpoint. Available plasma concentration of PF-05230907 will be descriptively summarized and plotted by nominal PK sampling time and dose group.

Pharmacodynamics Analysis

The pharmacodynamic endpoints include aPTT or PTT and PF1+2, within 2 days of dosing. These will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Safety Analysis

All subjects who received the treatment of PF-05230907 will be included for safety analysis.

Safety endpoints, including the primary endpoints of treatment emergent TIEs, AEs, SAEs, and laboratory abnormalities; physical examination and vital signs changes; ECG results and other safety data will be summarized descriptively by dose group. As discussed in Section 9.1, the TIE data from the current cohort will be utilized for the mCRM design along with clinical and eDMC oversight to determine the dose for the next cohort.

Immunogenicity Analysis

ADA, NAb and Factor X activity level will be summarized by dose and time points for samples tested. Subjects with ADA and NAb immune responses will be summarized by dose.

SCHEDULE OF ACTIVITIES

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

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

Protocol Activity	**Screening**	**Hospital Confinement**								**Outpatient Follow-Up**	
Visit Identifier	**Day 1**	**Day 1 Hr 0**	**Day 1 Hr 0 Min 5**	**Day 1 Hr 0 Min 45**	**Day 1 Hr 3 and Hr 9**	**Day 2 (24 hr)**	**Day 3 (48 hr)**	**Day 4 (72 hr)[a]**	**Day 8/discharge[b]**	**Day 43**	**Day 91**
Visit Window[c]	**Up to 6.0 Hr pre-dose**		**±2 min**	**±15 min**	**±30 min**	**±6 hours**	**±6 hours**	**±6 hours**	**±24 hours**	**±7 days**	**±7 days**
Informed consent[d]	X										
Demography	X[e]										
Medical history and smoking history	X[e]										
Medical Procedures											
Comprehensive physical examination	X								X		
Targeted physical exam						X	X	X			
Vital signs[f]	X		X	X		X	X	X	X		
Highest observed BP documentation[g]									X		
ECG (12-lead)	X					X		X	X		
Weight and height[h]	X										
Brain CT Scan	X					X		X[i]			
ICH Volume by ABC/2	X										
Doppler lower extremity ultrasonography	X[e]							X			
Safety Laboratory											
D-dimer-local lab	**X**							**X**	**X**		
Prothrombin G20210A Mutation	X[e]										

Protocol Activity	Screening	Hospital Confinement								Outpatient Follow-Up	
Visit Identifier	**Day 1**	**Day 1 Hr 0**	**Day 1 Hr 0 Min 5**	**Day 1 Hr 0 Min 45**	**Day 1 Hr 3 and Hr 9**	**Day 2 (24 hr)**	**Day 3 (48 hr)**	**Day 4 (72 hr)[a]**	**Day 8/discharge[b]**	**Day 43**	**Day 91**
Visit Window[c]	**Up to 6.0 Hr pre-dose**		**±2 min**	**±15 min**	**±30 min**	**±6 hours**	**±6 hours**	**±6 hours**	**±24 hours**	**±7 days**	**±7 days**
Factor V Leiden Mutation	X[e]										
TFPI	X										
Blood chemistry	X							X			
PT/INR[s]	X		X	X		X		X			
Fibrinogen[s]	X			X		X		X			
ATIII	X			X		X		X			
Protein S level	X			X		X		X			
Protein C activity	X			X		X		X			
Hematology[s]	X			X		X		X			
Cardiac troponin I (local or central lab)[t]	X				X	X	X	X			
Urinalysis	X[e]								X		
Pharmacodynamics											
aPTT/PTT	X		X	X		X		X			
PF1+2	X		X	X		X					
Exploratory biomarker	X		X	X		X		X			
Pharmacokinetics											
PK	X		X	X							
Immunogenicity											
ADA	X								X	X	X[j]
NAb	X								X	X	X[j]
FX activity	X								X	X	X[j]
Anti-CHO	X									X	
Anti-PACE	X									X	
Banked biospecimens											
Prep D1	X[e]										
Other biomarkers											
Exploratory biomarker(s) of neuro-inflammation	X					X	X	X			

Protocol Activity	Screening	Hospital Confinement								Outpatient Follow-Up	
Visit Identifier	**Day 1**	**Day 1 Hr 0**	**Day 1 Hr 0 Min 5**	**Day 1 Hr 0 Min 45**	**Day 1 Hr 3 and Hr 9**	**Day 2 (24 hr)**	**Day 3 (48 hr)**	**Day 4 (72 hr)[a]**	**Day 8/discharge[b]**	**Day 43**	**Day 91**
Visit Window[c]	**Up to 6.0 Hr pre-dose**		**±2 min**	**±15 min**	**±30 min**	**±6 hours**	**±6 hours**	**±6 hours**	**±24 hours**	**±7 days**	**±7 days**
Trial Treatment Procedures											
Review Inclusion/Exclusion Criteria	X										
Treatment Allocation	X										
Investigational product administration		X									
Discussion and documentation of contraception[k]									X	X	
Approval for release of health care information[l]									X		
Concomitant Medications	X[e]	→	→	→	→	→	→	→	→	→	
Concomitant Treatments	X[e]	→	→	→	→	→	→	→	→	→	
Adverse Events (AEs)			X	→	→	→	→	→	→[m]		
Serious Adverse Events (SAEs)	X	→	→	→	→	→	→	→	→	→	
Health resource utilization (HRU)[n]									X	→	→
Assessments											
Glasgow Coma Scale[o]	X[o]	X[o]		X							
Modified Rankin Scale (mRS)[p]	X					X		X		X	X
National Institute of Health Stroke Scale (NIHSS)[q]	X[e]			X		X		X		X	X
Thrombosis clinical probability scores[r]								X	X		

Abbreviations: → = ongoing/continuous event; ADA = anti-drug antibody; AEs = adverse events; Anti-CHO = anti-Chinese hamster ovary; anti-PACE = anti-paired basic amino acid cleaving enzyme; aPTT = activated partial thromboplastin time; ATIII = antithrombin III; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; FX = factor X; Hr = hour(s); HRU = health resource utilization; ICU = intensive care unit; IVH = intraventricular hemorrhage; Min = minute(s); MR = magnetic resonance; mRS = modified rankin scale; NAb = neutralizing antibody; PD = pharmacodynamic; PF1+2 = prothrombin fragment 1+2; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; SAEs = serious adverse events; TFPI = tissue factor pathway inhibitor.

a. Subjects in the study must stay in the hospital/stroke unit/ICU at a minimum through Day 4. If a subject is discharged on Day 4 see Section 6.2.8.

b. See Section 6.2.9 if subject was discharged prior to Day 8.

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

d. ICH related information from medical records (such as Glasgow Coma Scale [GCS] assessment by emergency medical services, CT scan and ICH characteristics, vital signs, ECG, physical examination, laboratory test results, demography, weight, medical history, concomitant medications, concomitant treatments) which is collected prior to the time of consent but within 6.0 hours of ICH symptom onset may be used to assist with inclusion/exclusion determination.

e. If the following cannot be collected during the Screening Day 1 period, the site may collect as soon as possible post-dose but prior to Day 4-see Section 6.1:

- Demography that does not affect eligibility (race and ethnicity).
- Prothrombin G20210A Mutation.
- Factor V Leiden Mutation.
- Urinalysis (if not collected pre-dose collect as soon as possible post-dose).
- Prep D1 banked biospecimen (unless prohibited by local regulations or ethics committee decision) and additional consent to allow banked biospecimen Prep D1 to be used for additional purposes (unless prohibited by local regulations or ethics committee decision).
- Medical history that does not affect eligibility.
  - The following medical history elements affect study eligibility and **must** be collected during the screening period: non-ICH related severe uncontrolled medical conditions, other severe acute and chronic medical and psychiatric conditions and laboratory abnormalities that may increase the risk associated with study participation; ischemic, vaso-occlusive and thrombotic events or conditions; prothrombotic disorders; thrombocytopenia; coagulopathy, acute sepsis, crush injury, and disseminated intravascular coagulation events or conditions; and hamster protein allergies.
- Concomitant medications taken within 7 days of study enrollment that do not affect eligibility. The following concomitant medication information affects study eligibility and **must** be collected during the screening period: oral anti-coagulant(s) [eg, warfarin or novel oral anticoagulant], low molecular weight heparin and heparin (except when used as catheter flush).
- Concomitant treatments within 7 days of study enrollment that do not affect eligibility.
- Doppler lower extremity ultrasonography.
- NIHSS.

f. If during hospital confinement period, the magnitude of a vital sign abnormality is sufficient to be reported as an AE then vital signs should be collected as a daily unscheduled observation during the hospital confinement period (eg, Day 5 through Day 8/discharge) and should be followed until the AE resolves or stabilizes-see Section 8.1.

g. The highest observed blood pressure result for each of the following Day 1 post-dose time intervals to be collected: hour 0-3, hour 3-6, hour 6-12, and hour 12-24 for a total of 4 collected highest observed BP results.

h. Subject reported weight measured within the last 3 months is acceptable if actual weight cannot be obtained. If subject reported weight is utilized, actual weight should be collected as soon as possible post-dose. Subject reported height is acceptable.

i. CT scan is the preferred imaging modality however for the Day 4 assessment a site may substitute an MR scan based on local standard of care (SoC), local regulatory, or clinical considerations at the investigator's discretion.

j. ADA, NAb and FX activity to be collected at Day 91 only if subject tested positive for antibody immune response at Day 43.

k. At the Day 8/discharge visit, a discussion of the birth control protocol specifications is to occur and is to be documented in male subjects' charts that are able to father children and are sexually active and at risk of pregnancy. The Day 43 visit will require documenting the birth control method utilized for male subjects who are able to father children and are sexually active and at risk of pregnancy-see Section 4.4.

l. Secure approval for release of health care information from study subject/legal guardian/legally acceptable representative as permitted by local, state, and institutional guidance to assist with collection of adverse events through Day 8 and collection of serious adverse events through Day 43.

m. Sponsor and investigator documentation of TIEs must occur at Day 8. Telephone follow-up call on Day 8 for collection of adverse events if subject was discharged prior to Day 8.

n. Health resource utilization information to be collected during the study include admission date of subject to the stroke unit/ICU, discharge date of the subject from the stroke/ICU unit, admission/discharge date of the subject from the hospital (if moved from stroke unit/ICU), date subject began in-patient rehabilitation, discharge date subject completed in-patient rehabilitation, date subject began out-patient rehabilitation, and discharge date subject completed out-patient rehabilitation.

o. See Appendix 5 for Glasgow Coma Scale. Screening GCS assessments to be collected include both an assessment by emergency medical services prior to hospital admission (if possible) and a bedside assessment by a study team member as soon as possible after arrival at the study site. The Day 1 / Hour 0 GCS should be performed immediately prior to dosing.

p. See Appendix 6 for mRS. Retrospective (prior to ICH) mRS completed at screening.

q. See Appendix 4 for NIHSS. Screening period NIHSS assessment should be performed within 2 hours prior to planned dosing and as close to time of dosing as is feasible.

r. See Appendix 2 for Thrombosis Clinical Probability Scores Assessment.

s. For sites in Germany, samples collected after Day 1, Hour 0 (post-dose) should also be analyzed locally.

t. For sites where only cardiac troponin T analysis is available at the local laboratory, cardiac troponin T results are allowed for the 72-hour safety data review for sequential dosing. Cardiac troponin I samples are still required and must be shipped to the central lab for processing.

1. INTRODUCTION

1.1. Indication

Spontaneous intracerebral hemorrhage (ICH) is a major cause of death and disability accounting for approximately 10-15% of stroke cases worldwide.[1,2] ICH continues to be associated with poor clinical outcomes, approximately 35-52% of patients die within one month, mortality at 6 months ranges from 23-58% and a large number of individuals fail to regain functional independence by six months.[1,3] The current management of ICH is largely supportive and the lack of effective treatment for ICH remains a critical and unmet need.

The investigational product PF-05230907, a variant of recombinant activated coagulation factor X (FXa) formerly known as $rFXa^{I16L}$, is being developed as a single dose treatment for patients with ICH.

This investigation product will be referenced only as PF-05230907 in all subsequent sections of this protocol document.

1.2. Mechanism of Action/Indication

FXa occupies a central position in the coagulation cascade between thrombin-generation and the intrinsic (Factor VIII/Factor IX dependent) and extrinsic (Factor VII/Tissue Factor dependent) pathways. Membrane-bound FXa, in the presence of its cofactor Factor Va (FVa), converts prothrombin to thrombin, which activates platelets and converts fibrinogen to fibrin to form a thrombus. FXa is the only activator of prothrombin. In principle, replacement therapy with direct FXa infusion could correct bleeding, however the therapeutic potential of FXa is limited due to a very short plasma half-life and a potential for excessive coagulation due to activation of other coagulation factors. Pfizer and its collaborators have identified a novel variant of coagulation FXa (PF-05230907) that may establish, without excessive thrombotic risk, localized hemostasis at the site of bleeding in a number of clinical situations of uncontrolled bleeding such as ICH.[4]

1.3. Background and Rationale

1.3.1. Nonclinical Safety Data

1.3.1.1. Nonclinical Pharmacology

In response to an injury, FVa is generated at the site of injury and the interaction of FXa with FVa leads to localized thrombin generation. PF-05230907 is a variant of FXa that has an isoleucine to leucine substitution at its 16 position (Chymotrypsin numbering) and is more protected from inactivation by serum protease inhibitors. It regains susceptibility to inactivation by serum protease inhibitors when activated by cofactor FVa, similar to native FXa.

PF-05230907 caused a dose-dependent shortening of clotting times in vitro in citrated pooled plasma from humans (CCI [redacted]), cynomolgus monkeys (EC_{50}=49 ng/mL; 1.1 nM), mice (EC_{50}=89 ng/mL; 1.93 nM), and rats (EC_{50}=91 ng/mL; 1.98 nM), as evaluated by measuring activated partial thromboplastin time (aPTT). Furthermore, in the thrombin generation assay, PF-05230907 caused a

dose-dependent increase in thrombin generation and a shortening of the lag time in plasma from humans [redacted]), monkeys (EC_{50}=17 ng/mL; 0.37 nM), mice (EC_{50}=5 ng/mL; 0.11 nM), and rats (EC_{50}=12 ng/mL; 0.27 nM). In the thrombin generation assay, the inactivation of Factor V/Va by the activated protein C (APC) pathway effectively regulated PF-05230907. In vitro treatment of platelets with PF-05230907 up to 4,600 ng/mL (100 nM) did not lead to platelet activation in vitro, as evaluated by aggregation and flow cytometry using antibodies as markers of platelet surface activation. PF-05230907 was efficacious in a number of in vivo models. Specifically, PF-05230907 shortened aPTT in FVIII-deficient dogs (at ≥0.1 μg/kg/day); decreased hemoglobin content in homogenized brain tissue (a marker of hematoma blood volume) from mice (50% effective dose [ED_{50}]=3.05 μg/kg) and rats (minimum effective dose [MED]=10 μg/kg) with collagenase-induced intracerebral hemorrhage; and decreased blood loss associated with tail transaction in mice (ED_{50}=46 μg/kg) and Sprague Dawley rats (ED_{50}=38 μg/kg). Additional information may be found in the Investigator's Brochure.

1.3.1.2. Nonclinical Pharmacokinetics and Safety Toxicology

PF-05230907 was not evaluated in stand-alone safety pharmacology studies. However, endpoints that evaluated for effects on the cardiovascular, central nervous system, and respiratory systems were included in the 3-day and 1-month good laboratory practices (GLP) toxicity studies in cynomolgus monkeys given PF-05230907 at twice daily (BID) doses approximately 8 hours apart. In these studies, there were no test article-related effects on electrocardiogram (ECG) parameters, blood pressure, heart rate, body temperature (only evaluated in the 1-month study), or effects on neurobehavioral or respiratory assessments at any dose tested.

It is known that endogenous FXa is rapidly inactivated by complex formation with plasma protease inhibitors such as, antithrombin III (ATIII), α2-Macroglobulin and α1-antitrypsin.[5] In a [^{125}I]-FXa study, two minutes after intravenous injection (IV), the majority of FXa was found to be bound with protease inhibitors and eliminated from the plasma by low-density lipoprotein receptor-related protein (LRP)-mediated clearance. Pharmacokinetics (PK)/toxicokinetics (TK) of PF-05230907 after a single and multiple IV doses were characterized in mice, rats and monkeys. PF-05230907, with high plasma protein binding, exhibits low volume of distribution, high clearance and a very short half-life. The terminal elimination half-life ranged from 4-9 minutes in mice, rats and monkeys. At non thrombogenic doses, the volume of distribution for PF-05230907 was small indicating that PF-05230907 is mainly confined in the intravascular fluid. Systemic exposure of PF-05230907 was generally dose-related; no accumulation of PF-05230907 was observed in cynomolgus monkey after repeat twice daily dosing (BID) for three days.

PF-05230907 was evaluated in single- and repeat-dose toxicity studies up to 1 month in duration in mice, rats, and monkeys; in a single-dose thrombogenicity study in rabbits; and in single- and/or repeat-dose biomarker studies in mice, rats, and monkeys and an in vitro biomarker study with human plasma. Pivotal studies were the 3-day studies in rats and monkeys. Administration of increasing doses of PF-05230907 resulted in a spectrum of events that ranged between findings consistent with pharmacologic effects at relatively low doses, findings consistent with exaggerated pharmacology and excessive thrombi/emboli

formation at higher doses, and findings consistent with consumptive coagulopathy at the highest doses. The primary effects of PF-05230907 observed in these studies were adverse thrombi/emboli in the lungs, heart, injection site/tail, kidney, and/or liver at ≥0.1 mg/kg/day in monkeys, ≥0.04 mg/kg/day in mice, ≥0.6 mg/kg/day in rats, and ≥0.06 mg/kg in rabbits. The incidence and severity of thrombi/emboli formation was dependent upon the dose and duration of dosing. In monkeys given 0.1 to 0.5 mg/kg/day, thrombi/emboli were not associated with clinical signs, but were associated with shortened followed by prolonged aPTT, increased thrombin-antithrombin (TAT), and marked decreases in protein C and fibrinogen. However results from an in vitro study indicate that the pharmacological activity of PF-05230907 can interfere with Protein C measurements in human plasma when evaluated with the Staclot assay.[6] In monkeys given ≥3 mg/kg/day, some animals were electively euthanized due to findings consistent with consumptive coagulopathy which included an inability to stop bleeding at blood collection sites despite applying pressure for a prolonged period of time (up to 1 hour), marked decreases in platelets and fibrinogen, prolongation of prothrombin time (PT), and microscopic findings of hemorrhage at the injection site that penetrated into the adjacent subcutaneous tissue and muscle. In mice and rats, transient tail discolorations occurred at ≥0.04 mg/kg/day (mice) and at 2 mg/kg/day (rats). The No Observed Effects Level (NOEL) for thrombi/emboli and the No Observed Adverse Effect Level (NOAEL) for PF-05230907 when administered for 3 days were 0.3 mg/kg/day in rats and 0.05 mg/kg/day in monkeys.

1.3.2. Clinical Experience with PF-05230907

To date, a single clinical study has been conducted with PF-05230907. The clinical program for PF-05230907 was initiated in September 2013 with a Phase 1 first in human, randomized, double-blind, sponsor-open, placebo-controlled study (B2341001) evaluating the safety, tolerability, PK and pharmacodynamic (PD) of escalating single doses of PF-05230907 in healthy adult subjects age 18 to 35 with no demographic, acquired or hereditary prothrombotic risk factors. This completed study enrolled 49 male subjects at a single site. PF-05230907 was sequentially evaluated at dose levels of 0.1, 0.3, 1.0, 2.0, 3.0 and 5.0 μg/kg and subjects in the respective cohorts were randomized to receive either PF-05230907 or placebo at a ratio of 6:2. All dose levels evaluated in this study were safe and well tolerated and evidence of pharmacologic activity was observed. The following data represent the completed study results.

There were no deaths, no serious adverse events (SAEs), or discontinuations reported in the study. Treatment emergent adverse events (TEAEs) in PF-05230907 treated subjects were mild in severity (23/28) or moderate in severity (5/28) and there were no severe TEAEs or withdrawals due to TEAEs. There did not appear to be any dose-related trends in frequency of TEAEs across the dose levels of PF-05230907 or placebo. Of the 37 subjects in the 6 treatment groups who received PF-05230907, 1 subject experienced a treatment-related TEAE. This single treatment-related TEAE was headache, classified as mild in severity, and reported in the 5 μg/kg treatment group. Thrombosis and pulmonary embolus clinical probability assessments were performed for all subjects and were scored as low probability for all subjects at all assessments.

There were no clinically significant changes from baseline in vital sign (blood pressure, pulse rate, oral temperature and respiration rate) measurements, 12-lead electrocardiogram (ECG) parameters or physical examinations noted in individual subjects or within treatment groups.

Treatment emergent changes in clinical safety laboratory values were generally small and sporadic, with no clinically significant changes in hematology including platelet count, PT/INR, fibrinogen, ATIII, cardiac troponin I, or D-dimer (Day 7 and on). Dose dependent modulation of Protein C and Protein S activity, when analyzed with a clot based assay, were observed. Non-clinical studies indicate these changes reflect pharmacologic activity of the drug.[6] Protein C activity and free Protein S level measured using non-clot-based assays for the 3 and 5 μg/kg dose groups showed no treatment-related reduction. No subject had an adverse event (AE) related to abnormal laboratory test results and no subject met the pre-specified stopping rule criteria.

One weak and transient anti-drug antibody (ADA) response was detected in one subject from the 3 μg/kg cohort at a single time point of Day 29. ADA results for the same subject on Day 1 (baseline), Day 15, Day 43, and the 6 month follow-up were negative. The positive anti-drug antibody did not cross react with native factor X or factor Xa and had no neutralizing activity. Based on all the available data, the sponsor, investigator, and the study eDMC determined that this finding did not alter the benefit risk profile of PF-05230907 for the intended indication of intracerebral hemorrhage.

Based on the PK data for all the subjects enrolled in the study, peak plasma concentration of PF-05230907 (C_{max}) was reached between 2 to 5 minutes post-dose and PF-05230907 concentration declined very rapidly thereafter. In all subjects except one (from the 5 μg/kg dose group), plasma PF-05230907 concentration was non-detectable by 40 minutes after dosing. The terminal half-life was calculated for 3 and 5 μg/kg, which are 4.6 (coefficient of variation [CV] =8%) and 3.7 (CV=2%) minutes respectively. Exposure appeared to increase dose-proportionally, especially at the higher doses where PK can be characterized more accurately. The very fast clearance of PF-05230907 is consistent with the observations in non-clinical studies.

Dose-dependent PD changes including plasma aPTT, plasma prothrombin fragment 1+2 (PF1+2), plasma thrombin-anti-thrombin complex (TAT) and plasma D-dimer were observed in study B2341001. Maximum aPTT shortening occurred between 2 to 5 minutes coincident with maximal exposure and returned to baseline by 2 hours at all dose levels. At the highest tested dose (5 μg/kg), median maximum aPTT shortening was 8.92 seconds. PF1+2, TAT and D-dimer are in vivo biomarkers and their increases were delayed compared with aPTT and the durations of change were prolonged compared with PK exposure.

Please refer to the Investigator's Brochure for more detailed information.

1.4. Study Rationale

This study will determine the maximum tolerated dose (MTD) of PF-05230907 and evaluate safety and tolerability of a single administration of PF-05230907 in subjects with spontaneous intracerebral hemorrhage (ICH). Given the severe morbidity and mortality associated with the condition and given the need to better define the maximum tolerated dose of PF-05230907 in order to plan future efficacy studies, a modified continual reassessment method (mCRM) will be implemented to determine the MTD (see Section 9) based on frequency of treatment emergent thromboembolic and/or ischemic events (to be referred to as TIEs throughout this document). A target TIE rate of 15% represents approximately a 5-10% increment above the background rate and is considered compatible with acceptable benefit risk in the high morbidity, high mortality indication of ICH. A background rate of approximately 5-10% in the ICH population is based upon published literature for spontaneous ICH from studies of activated coagulation factor VII in ICH and the placebo-treated subject-level datasets from 4 studies performed contemporaneously with the clinical studies of NovoSeven in ICH contained within the Virtual International Stroke Trial Archive (VISTA).[7,8,9] The TIE rate in the internal analysis of the VISTA placebo datasets filtered to reflect the intended population for treatment with PF-05230907, was approximately 5.5% within the first 8 days from the baseline computed tomography (CT) scan.

Selection of the PD biomarkers included in the study (aPTT and PF1+2) is informed by the results from the study B2341001. The PD results will provide information on target engagement and coagulation pathway activation at the various dose levels studied.

1.5. Dose Rationale

The starting dose planned for this study is 5 µg/kg, which is the highest dose level tested that was safe and tolerated in the Phase 1 first-in-human (FIH) study of PF-05230907 in healthy volunteers (B2341001). Based on the data from Study B2341001, C_{max} of 46.13 ng/mL and AUC_{last} of 5.452 ng•h/mL at this dose have a [redacted]-fold and [redacted]-fold safety margin respectively in comparison to the exposure at the NOAEL in monkeys [redacted], AUC_{last} was [redacted]; and a [redacted]-fold and [redacted]-fold safety margins respectively in comparison to the exposure at the NOAEL in rats [redacted]

For this study, a pre-specified dose grid (Table 1) will be used for dose assignments based on the mCRM algorithm. Beginning from the starting dose of 5 µg/kg, the mCRM dose grid will be in increments of approximately 25-30%. The dose increment step is based on the variability of PK observed in Study B2341001.

The highest dose for this study will be established based on safety observed during the study and therefore cannot be pre-specified. For purposes of implementing the mCRM assessment of MTD, the proposed maximum dose is 47 µg/kg (see Section 3), which is predicted to have approximately twice the exposure for both C_{max} and AUC at NOAEL in monkeys which is the more sensitive species compared with rats (Table 1). The NOAEL is established in monkeys based on 3 days of BID dosing in the pivotal toxicity studies while in this study (B2341002), only a single dose is planned for administration. The condition of ICH is

associated with substantial morbidity and mortality and, as is the case for other high mortality conditions, cautious dose escalation beyond the NOAEL can be justified. In ICH a modest increase above the background rate of treatment emergent thromboembolic or ischemic events is compatible with favorable benefit risk for a potentially efficacious hemostatic agent.

To mitigate potential risk from dose escalation beyond exposure at the NOAEL in monkeys, dose escalation will be conducted in a limited number of subjects per cohort (N=3), sequential dosing of subjects will be implemented in each cohort evaluating a dose level that exceeds previously administered dose levels, and dosing will be paused following completion of each cohort until safety is assessed for the respective cohort. As described below (see Section 3), dose escalation will take place in limited increments. The increments may be further reduced based on results from laboratory safety parameters, clinical safety observations, eDMC recommendations and continuous integration of safety data into the mCRM model. In summary, the severity of the condition of ICH in combination with the measures for monitoring subject safety, the limited increments in dose escalation and the limited number of subjects exposed in each dosing cohort provide justification for cautious dose escalation that may exceed exposure at the NOAEL in monkeys.

If the 47 µg/kg dose is well tolerated and the MTD has not been established, the protocol may be amended and submitted to ethics committees and to regulatory authorities as required to permit evaluation of a higher dose(s). Predicted exposure and safety margin compared with exposure at the NOAEL for monkeys, the more sensitive species, at the potential dose levels to be tested in the study are presented in Table 1.

Table 1. Predicted Exposure and Margins Relative to Toxicokinetic Limit

Proposed Human Dose (µg/kg)	Predicted Human PK[a] C_{max} (ng/mL)	Predicted Human PK[a] AUC (ng·h/mL)	Safety Multiple Based on Monkey NOAEL Dose of 0.025 mg/kg/dose[b] C_{max} = 229 ng/mL	Safety Multiple Based on Monkey NOAEL Dose of 0.025 mg/kg/dose[b] AUC = 22.9 ng·h/mL
1	9.23	1.09	24.8	21.0
2	18.45	2.18	12.4	10.5
3	27.68	3.27	8.3	7.0
4	36.90	4.36	6.2	5.3
5	46.13	5.45	5.0	4.2
6	55.36	6.54	4.1	3.5
8	73.81	8.72	3.1	2.6
10	92.26	10.90	2.5	2.1
12	110.71	13.08	2.1	1.8
15	138.39	16.36	1.7	1.4
19	175.29	20.72	1.3	1.1
24	221.42	26.17	1.0	0.9
30	276.78	32.71	0.8	0.7
37	341.36	40.34	0.7	0.6
47	433.62	51.25	0.5	0.4

[a] Prediction based on dose linear extrapolation from the values observed at 5 µg/kg from Study B2341001.
[b] NOAEL established from 3 day BID dosing study in monkey.

1.6. Anticipated Risks and Safety Monitoring

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure.

Human experience with PF-05230907 is limited to Phase 1 Study B2341001. There are no identified adverse drug reactions to PF-05230907. Potential risks are based on clinical and toxicology data.

Possible risks for PF-05230907 include the potential for thromboembolic and ischemic complications and the potential for immunogenicity including, but not limited to, infusion reactions, anaphylaxis, and formation of ADA which may affect functions of endogenous FXa and FX. Although the possibility of ADA development is considered to be low to moderate, the perceived immunogenicity risk of PF-05230907 is considered to be high based on the severe consequence that the ADA may affect function of endogenous FXa and FX.

1.6.1. Summary of Risk Benefit

Based on the potential risks, subjects will be monitored for the following treatment emergent parameters: laboratory, vital sign, physical examination and ECG abnormalities and adverse events including TIEs. Monitoring will also include the Wells Thrombosis Probability Assessments (Appendix 1), a CT or magnetic resonance (MR) scan of the brain at 72 hours, and Doppler ultrasonography of the lower extremities at 72 hours. Monitoring for antibody immune response will use a tiered testing strategy including measurement of ADA to PF-05230907 and further characterization of any positive anti-body immune responses such as testing for neutralizing antibody (see Section 9.6.1).

PF-05230907 is being developed as a single administration treatment of the life threatening condition ICH, wherein affected patients incur substantial mortality and long term morbidity.

Safety was demonstrated at all tested dose levels up to 5 μg/kg in Phase 1 Study B2341001 and there did not appear to be any dose-related trends in frequency of reported treatment emergent adverse events. Possible risks from treatment with PF-05230907 include the potential for thromboembolic and ischemic events, hypersensitivity reaction, antibody immune response with formation of anti-drug antibodies. These risks are believed to be manageable because: 1) thrombi/emboli formation was reversible in animals, 2) changes in coagulation parameters/biomarkers in monkeys that were associated with the presence or absence of thrombi/emboli can be monitored in the clinical setting, and 3) the potential toxicity of thrombi/emboli, hypersensitivity response and antibody immune response is considered compatible with acceptable benefit/risk in the life-threatening and severely disabling condition of ICH.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective:

- Based on the mCRM algorithm, determine the maximum tolerated dose (MTD) of PF-05230907 administered once as an IV bolus in subjects with ICH.
- Determine the overall safety and tolerability of PF-05230907.

Secondary Objectives:

- Evaluate PD effects of treatment with PF-05230907.
- Determine the frequency of antibody immune response to PF-05230907.

Exploratory Objectives:

- Assess hemostatic efficacy of PF-05230907.
- Characterize the PK profile of PF-05230907.
- Assess effect of PF-05230907 on exploratory biomarkers of PD in subjects with ICH.
- Assess potential measures of neuro-inflammation and/or neurologic outcomes in subjects with ICH.
- Assess brain imaging parameters that may be associated with efficacy or safety of treatment with PF-05230907 and/or outcomes in ICH.
- Determine frequency of antibody immune response against proteins from host cells used in manufacture of PF-05230907.
- Assess neurological outcome measures.
- Assess health resource utilization.

2.2. Endpoints

Primary Endpoint:

- Frequency of treatment emergent thromboembolic and/or ischemic events (TIEs) in subjects treated with PF-05230907 through Day 8.
- Treatment emergent serious adverse events as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 43.

- Treatment emergent adverse events as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 8.
- Treatment emergent laboratory abnormalities as characterized by type, frequency, and severity through Day 4 (Day 8/discharge for D-dimer).
- Physical examination changes through Day 8 (or discharge).
- Vital sign changes through Day 8 (or discharge).
- ECG results through Day 8 (or discharge).

Secondary Endpoints:

- Changes in aPTT and PF1+2 after dosing with PF-05230907 through Day 2.
- ADA/neutralizing antibody (NAb) and Factor X activity through Day 43 and/or Day 91 follow-up visit.

Exploratory Endpoints:

- ICH absolute and percent change from baseline volume at 24 hours (see SOA).
- PF-05230907 concentration in plasma.
- Change in other exploratory biomarkers that may reflect pharmacologic effect of PF-05230907 or ICH progression may be evaluated.
- Potential biomarkers of neuro-inflammation and/or neurological outcomes to better understand ICH and/or its outcomes.
- CT parameters that may inform future investigations of PF-05230907 and/or the condition of ICH.
- Anti-Chinese hamster ovary (CHO) protein antibodies.
- Anti-paired basic amino acid cleaving enzyme (PACE) furin antibodies.
- Neurologic function as assessed by the NIHSS.
- Surrogate measures for health resource utilization, may include duration of stay in stroke/ICU unit, duration of hospital stay, duration of inpatient rehabilitation, and duration of outpatient rehabilitation.

Some of the planned biomarker(s) may not be performed if not supported by data from the ongoing pre-clinical work.

3. STUDY DESIGN

This is a Phase 1b, multi-center, open-label study to determine the maximum tolerated dose (MTD) and assess the safety and tolerability, and PD of PF-05230907 administered once as an IV bolus in subjects with ICH. A modified continual reassessment method (mCRM) design based on the endpoints of treatment emergent thromboembolic and/or ischemic events (TIEs) will be adopted. The mCRM design utilizes Bayesian methodology to continuously learn the dose-toxicity relationship, which is characterized by a parametric model. The starting dose will be 5 μg/kg based on the highest dose safely administered in the first in human (FIH) clinical study (B2341001).

As safeguards for subject safety, (a) dose escalation will be conducted in a limited number of subjects per cohort (N=3), (b) sequential dosing of study subjects will be implemented in each cohort evaluating a dose level that exceeds previously administered dose levels and rules will apply governing additional cohorts at the respective dose level that are subject to sequential dosing (section 3.1), (c) dosing will be paused following completion of each cohort until safety is assessed for the respective cohort, (d) safety laboratory biomarker criteria are implemented which trigger smaller maximum increments for dose escalation (Section 3.2) (e) enrollment of the next cohort will not proceed until a safety review has completed for the preceding cohort and the chair of the eDMC has provided authorization (Section 3.3) and (f) criteria are implemented which trigger an automatic eDMC review of safety at a respective dose level (Section 3.3).

3.1. Sequential Dosing

Sequential dosing of subjects will be implemented in each cohort evaluating a dose level that exceeds previously administered dose levels. An enrollment pause will be implemented following dosing of each subject in the cohort to allow for medical monitor safety data review prior to dosing the next subject. For the safety review that will take place during the enrollment pause, clinical observation results collected on the respective subject during the initial 72-hour period following dosing (treatment emergent adverse events [TEAEs], SAEs, vital sign changes, electrocardiogram [ECG] changes, Brain imaging study [CT ± MRI] scan, Doppler ultrasound of the lower extremity and cardiac troponin I [and cardiac troponin T, where applicable]) will be reviewed by the medical monitor. Other available laboratory test results at the time of this safety review will also be assessed.

If a Suspected Unexpected Serious Adverse Reaction (SUSAR) or 2 or more grade 3 or higher adverse events that are considered at least possibly related to treatment with PF-05230907 are observed in the initial cohort evaluating a dose level that exceeds previously investigated dose levels, then the subsequent (second) cohort evaluating the respective dose level will also be subject to sequential dosing restrictions.

Severity of adverse events (AEs) and serious adverse events (SAEs) will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[10] TIEs will be defined as any of the listed events at the respective severity grade indicated in Appendix 1. All subjects who receive PF-05230907 are evaluable for TIEs. The determination of MTD using mCRM dose-toxicity modeling will be based on TIEs which occur through 7 days post-dose (Day 8).

3.2. Progression to Subsequent Cohort

A target 15% TIE rate at the MTD will be employed for the MTD determination. The range of doses that may be explored will be from a grid of doses ranging from 1 μg/kg to 47 μg/kg (Table 2). Subjects will be enrolled in cohorts, starting with an initial dose of 5 μg/kg for the first cohort (the highest dose safely administered in the first in human clinical study [B2341001]). If the modeled rate of TIEs at the 5 μg/kg starting dose exceeds the pre-specified target toxicity rate of 15% for the MTD, lower doses may be explored. Starting with the second cohort, subjects will be assigned to a dose in the pre-defined dose grid that is closest to, but not exceeding, the currently predicted MTD based on a parametric dose-toxicity model that the mCRM utilizes to learn about the overall dose-TIE relationship subject to additional dose escalation constraints and clinical oversight. The dose-toxicity model is updated based on the frequency of TIEs in each completed cohort. Under the adopted mCRM design, the dose level for each subsequent cohort can be escalated, deescalated, or restudied but always aiming towards the MTD target based on the frequency of TIEs. However, dose level assignments may be modified to more conservative dose levels based upon sponsor medical judgment or eDMC recommendations. To prevent overly aggressive dose-escalation, the maximum allowed dose increase from the highest dose that has been previously studied is limited to 2 increments at a time (ie, not more than one dose level may be skipped-see (Table 2), which results in 50-67% increase in dose from the 5 μg/kg dose and above. If treatment emergent modulation of one or more of the following laboratory safety biomarkers is observed during the interval from baseline to Day 4 (where available), as indicated below, dose increase will be limited to only 1 increment at a time (ie, no more dose skipping):

- Fibrinogen:
    - If baseline value is within normal reference range: a post-dose value ≤50% of the lower limit of normal.
    - If baseline value < lower limit of normal reference range: a post-dose value ≤50% of the baseline value.
- Platelet Count:
    - If baseline value is within normal reference range: a post-dose value of <100,000.
    - If baseline value < lower limit of normal reference range: a post-dose value ≤50% of the baseline value.
- PT: a post-dose value that is prolonged by >4 seconds above the baseline value.

In addition to TIEs and available safety biomarkers data, other available safety data (including clinically significant AEs or SAEs) will also be assessed. These events will not have any impact on mCRM-determined dose recommendations but may be used to inform dose assignments more conservative than those derived by the dose-toxicity model. An enrollment pause will occur after each respective cohort completes dosing until the following are completed; sponsor review of the available safety data through Day 8 (or discharge) post-dose administration, discussion with the investigator(s)/sub-investigator(s) for each subject in the respective cohort, submission of an interim review memo including all 7-day safety data to the eDMC chair (or designee), authorization to proceed with enrollment from the eDMC chair (or designee), mCRM-determined dose recommendation, and adjustment of mCRM-determined dose to more conservative dose levels when deemed appropriate by the sponsor or eDMC. Additional detail of the safety assessment process is discussed in Section 7.1.

3.3. eDMC Review of Cohort Safety Data

The eDMC will be responsible for ongoing cumulative reviews of the study safety data (Section 9.8). In addition, progression to each subsequent cohort of study subjects will not occur until an interim review memo including all specified 7-day safety data has been provided to the eDMC chair (or designee), the mCRM-determined dose recommendation or adjustment of mCRM-determined dose to more conservative dose levels (when deemed appropriate by the sponsor) and authorization has been received from the eDMC chair (or designee) to proceed with enrollment of the subsequent cohort. At the discretion of the eDMC chair (or designee), the eDMC may direct that dosing at the respective dose level (or higher dose levels) be paused until a full meeting of the eDMC has been convened. If a Suspected Unexpected Serious Adverse Reaction (SUSAR) or 2 or more grade 3 or higher adverse events that are considered at least possibly related to treatment with PF-05230907 are observed in the initial cohort evaluating a dose level that exceeds previously investigated dose levels, then dosing at the respective dose level (and at higher dose levels) will be paused until a meeting of the eDMC has been convened.

3.4. Stopping Rules for mCRM Algorithm

Study enrollment will stop if (1) the maximum sample size has been achieved (51 subjects), (2) 12 subjects have been accumulated on a dose that is predicted to be the MTD by the fitted dose-toxicity curve or (3) all doses appear to be overly toxic and the MTD cannot be determined in the current trial. Available doses and percentage increments between doses corresponding to possible dose-escalation steps (1, or 2 at a time) are summarized in the table below (Table 2). Note that a particular dose-assignment sequence and number of subjects treated at each dose cannot be pre-specified in advance due to the dynamic nature of the Bayesian allocation procedure, and not every dose listed will be actually studied. Doses will be limited to the maximum that has been specified in Section 1.5.

Subjects who withdraw prior to Day 8/discharge may be replaced at the discretion of the Sponsor. Additional subjects may be added to one or more cohorts to further define the MTD or safety of PF-05230907.

3.5. Duration of Study Participation

The total length of time planned for study participation is approximately 3 months; 6.0 hours for screening, a single dose administration with a 4 day minimum hospital confinement period and follow-up visits through Day 91.

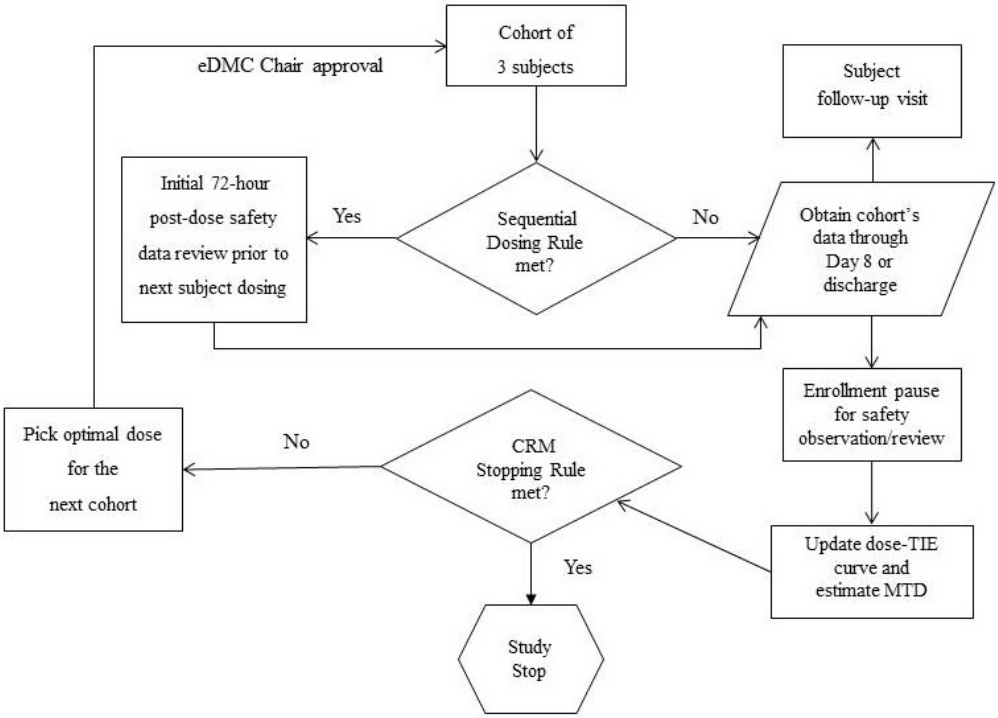
Table 2. Dose Escalation Schema

Dose (µg/kg)	Increment from prior dose	
	Escalation = increment of 1 dose level	Escalation = increment of 2 dose level (skipped dose)
1		
2	100%	
3	50%	200%
4	33%	100%
5*	25%	67%
6	20%	50%
8	33%	60%
10	25%	67%
12	20%	50%
15	25%	50%
19	27%	58%
24	26%	60%
30	25%	58%
37	23%	54%
47	27%	57%

* The starting dose is 5 µg/kg. If the TIE rate at the starting dose exceeds the pre-specified limit for the MTD, lower doses in the dose grid may be explored.

The following (Figure 1) is a schematic of the general Bayesian mCRM design incorporating the sequential dosing decision process.

Figure 1. mCRM Design Schematic



4. SUBJECT SELECTION

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

ICH related information from medical records (such as Glasgow Coma Scale [GCS] assessment by emergency medical services, CT scan, vital signs, ECG, physical examination, laboratory test results, demography, weight and height, medical history, concomitant medications, concomitant treatments) which is collected prior to the time of consent but within 6.0 hours of ICH symptom onset may be used to assist with the inclusion/exclusion determination.

CT scan completed and assessed by the investigator/designee within 6.0 hours from subject's symptom onset and prior to informed consent may be utilized for this study for purposes of determining study eligibility and to provide a baseline assessment of ICH volume (by ABC/2 method).

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative/legal guardian, in countries where it is accepted) has been informed of all pertinent aspects of the study.

   For sites in Sweden, only subjects that comply with the criteria specified in Appendix 8 may consent for the study.

2. Reasonable likelihood subject will comply with scheduled visits, laboratory tests, and other study procedures.

3. Male and/or female subjects (female subjects must be of non-child bearing potential) between the ages of 18 and 79 years of age.

   Female subjects who are of non-childbearing potential are defined as meeting at least 1 of the following criteria:

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure; or
   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

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

4. ICH as documented by CT scan within 6.0 hours of symptom onset.

5. Baseline ICH volume >5 mL and <60 mL based on the ABC/2 method (see Appendix 3).

6. At the time of treatment allocation, capability to treat with investigational product within 6.0 hours of symptom onset.

7. Body Mass Index (BMI) must be ≤40 kg/m^2.

4.2. Exclusion Criteria

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

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

2. Known participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

3. Non-ICH related known presence of severe uncontrolled medical condition(s), or other known severe acute or chronic medical or psychiatric condition(s) 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.

4. Pregnant female subjects; breastfeeding female subjects; male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the active treatment period (Day 1) and for 28 days after the single dose of investigational product.

5. Deep coma defined as Glasgow Coma Scale (GCS) score of 3-5 (see Appendix 5).

6. Prior disability defined as a modified Rankin Score (mRS) of >3 prior to ICH onset (see Appendix 6).

7. Known history of ischemic, vaso-occlusive or thrombotic events or conditions within 6 months prior to screening.

8. Known prothrombotic disorders.

9. Known secondary ICH related to aneurysm, arteriovenous malformation, subarachnoid hemorrhage, trauma, or other causes. CT angiography, MR, or other diagnostic studies obtained as part of the standard of care may be used to assess eligibility.

10. Known thrombocytopenia.

11. Known history of coagulopathy, acute sepsis, crush injury, or disseminated intravascular coagulation within 2 weeks prior to screening.

12. Subjects in whom surgical intervention is considered likely.

13. Known tumors of any etiology, except for basal or squamous cell carcinoma which has been treated and fully resolved for a minimum of 5 years.

14. Known use of oral anticoagulant(s) (eg, warfarin or novel oral anticoagulant).

15. Known use of low molecular-weight heparin (LMWH) or heparin (except when used to flush intravenous catheters).

16. Planned use of thrombolytic agents.

17. Known or suspected allergy to hamster protein.

4.3. Randomization Criteria

Subjects who meet the inclusion and exclusion criteria cannot be allocated to treatment unless there is an open study cohort at the intended time of allocation.

4.4. Lifestyle Guidelines

All male subjects who are able to father children and are sexually active and at risk for pregnancy must agree to use with their partner(s) a highly effective method of contraception consistently and correctly for the duration of the active treatment period (Day 1) and for at least 28 days after the single dose of investigational product. The investigator or his or her designee, will discuss with the subject the need to use highly effective contraception from the permitted list of contraception methods (see below) consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject 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 spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

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

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

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

    - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
    - Have medically confirmed ovarian failure; or
    - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause.

4.5. Sponsor's Qualified Medical Personnel

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

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

4.6. Rater Qualifications

4.6.1. ABC/2

The ABC/2 assessment of ICH volume will be completed by a trained physician. Training to conduct the ABC/2 will be provided by the sponsor or sponsor designee. Upon completion, documentation of training will be retained at the study site. If a physician holds ABC/2 certification from a previous study and the certification was received within 2 years, the study team will review for potential certification acceptance.

4.6.2. Neurologic Functional Assessments

4.6.2.1. Modified Rankin Score (mRS)

The mRS will be completed by a trained physician, trained physician assistant, trained nurse practitioner or equivalent as acceptable according to local regulation. Training to conduct the mRS will be provided by the sponsor or sponsor designee. Upon training completion, certification will be provided to the trained individual and should be retained at the study site. If a physician, physician assistant, nurse practitioner or equivalent holds mRS certification from a previous study and the certification was received within 2 years, the study team will review for potential certification acceptance.

4.6.2.2. Glasgow Coma Scale (GCS)

The GCS will be completed by a trained physician, trained physician assistant, trained nurse practitioner or equivalent as acceptable according to local regulations.

4.6.2.3. National Institutes of Health Stroke Scale (NIHSS)

The NIHSS will be conducted by a physician, trained physician assistant, nurse practitioner or equivalent as acceptable according to local regulation. The training will be provided by the sponsor or sponsor designee. Upon training completion, documentation of training in the respective endpoints will be retained at the study site.

5. STUDY TREATMENTS

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

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]/interactive voice response [IVR] system). Allocation of subjects to treatment groups may be paused between cohorts to permit safety assessments that inform future dose assignments. The dispensing personnel will be required to enter or select information including but not limited to the user's ID and password, the protocol number, the subject number and the date of birth of the subject. The dispenser will then be provided with a treatment assignment. The IRT system will provide a confirmation report containing the subject number. The confirmation report must be retained by the dispenser in the site files.

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

Note: The IRT system will provide the subject number at the end of the first IRT subject transaction.

5.2. Subject Compliance

Study treatment will be administered under the supervision of investigator site personnel.

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

PF-05230907 CCI [redacted] for Solution for Injection and diluent for PF-05230907 Powder for Solution for Injection will be provided by Pfizer Worldwide Research and Development (PWRD) as a lyophilized powder in single-use, sterile vials. The lyophilized placebo vial has been developed specifically for PF-05230907 and will be used after reconstitution with CCI [redacted] as a diluent for lower dose preparation as may be required per the dosage and administration instructions described in the Investigational Product Manual. In the remainder of the protocol diluent for PF-05230907 Powder for Solution for Injection will be referred to as diluent. Both PF-05230907 and diluent vials contain a white uniform cake.

PF-05230907 is supplied in a 6 mL clear glass tubing vial sealed with a coated rubber stopper and an aluminum seal with flip off cap. Each vial of PF-05230907 is designed to be reconstituted CCI [redacted]. The reconstituted solution of PF-05230907 has an extractable dose of CCI [redacted] as indicated on the label and is clear in appearance.

Diluent is supplied in a 6 mL clear glass tubing vial sealed with a coated rubber stopper and an aluminum seal with flip off cap. It is designed to be reconstituted with CCI [redacted] CCI [redacted]. The reconstituted solution of diluent has a nominal volume CCI [redacted] and is clear in appearance.

Sterile vials will be supplied as individual vials for reconstitution and subsequent unit dosing preparation.

PF-05230907 and diluent will be packaged as open-label supplies. Each carton will contain a single vial of study medication and ancillary items which include one 13 mm vial adapter and one infusion set with suitable hypodermic needle, as described in the Investigational Product Manual. Each carton will be packaged with a tamper-resistant seal. The sponsor must be notified of any study medication in which the tamper-resistant seal has been broken and this medication should not be used.

Further details will be detailed in the Investigational Product Manual.

Ancillary supplies used to prepare and administer doses are expected to be provided by the clinical site conducting the study unless otherwise agreed by the sponsor. Further guidance will be detailed in the Investigational Product Manual.

5.3.2. Preparation and Dispensing

PF-05230907 and vials labeled as diluent (if necessary based on dose) will be reconstituted CCI [redacted] using a 13 mm vial adapter as outlined in the Investigational Product Manual. Depending on the total dose required for a subject, one diluent vial may be required for dilution of the investigational product to prepare an appropriate concentration of the final dosing solution. The appropriate dose will be drawn up into an individual dosing syringe for administration.

The investigational product should be prepared and dispensed by appropriately qualified and experienced members of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. All dosage and administration calculations and dose preparation must be performed and checked by one clinical site personnel and verified by a second clinical site personnel. One of these two individuals must be a licensed health care professional. Dose preparation must be performed with locally accepted sterile handling technique. See the dosage and administration instructions in the Investigational Product Manual for instructions on how to prepare the investigational product for administration.

Appropriately qualified and experienced members of the study team who will prepare and dispense the investigational product, will receive study specific training on the obligations of the role and will sign an agreement that will be maintained in the Site Master File.

5.4. Administration

Subject should not be treated with study drug if more than 6.0 hours have elapsed since onset of ICH symptoms. Investigator site personnel will administer investigational product as a single IV bolus on Day 1. Consult the dosage and administration instructions in the Investigational Product Manual for detailed instructions regarding administration, permitted flush solutions and timing. The start and stop time of administration will be recorded. Time 0 is the time when investigational product administration begins.

Following preparation of the investigational product (PF-05230907) by the appropriately qualified and experienced member of the study team, the investigational product treatment will be administered to the subject.

5.5. Investigational Product Storage

The investigator, or an approved representative, (eg, pharmacist) will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Upon receipt at the study site, the investigational product (PF-05230907 and diluent) must be stored in a 2 to 8°C temperature-monitored refrigerator and in the original carton, according to labeled storage conditions. The investigational product and diluent cannot be used after the expiration date on the label.

Investigational product should be stored in its original container and in accordance with the label. See the Investigational Product Manual for storage conditions of the product once reconstituted and/or diluted.

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

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site locations in which study products will be stored (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product and diluent receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery.

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of the temperature range described in the labeling are not considered excursions.

5.6. Investigational Product Accountability

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

5.6.1. Destruction of Investigational Product Supplies

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

5.7. Concomitant Treatment(s) and Medication(s)

- Subjects will abstain from all prohibited concomitant treatments and medications, except if required for the treatment of AEs.

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

- Concomitant treatments and medications taken within 7 days prior to study enrollment will be documented as prior treatments and medications. Treatments and medications taken after Day 1 Hour 0 (post-dose administration) will be documented as concomitant treatments and medications.

5.7.1. Prohibited Prior Treatments and Medications

- Known use of oral anticoagulant(s) [eg, warfarin or novel oral anticoagulant];

- Known use of low molecular-weight heparin (LMWH) or heparin (except when used to flush intravenous catheters);

- Known use of investigational drug(s) within 30 days prior to screening;

- Experimental treatment(s) and/or medication(s) within 30 days prior to screening.

5.7.2. Prohibited During the Study

- Oral anticoagulant(s) [eg, warfarin or novel oral anticoagulant];

- LMWH or heparin at therapeutic doses;

    - After documentation of cessation of bleeding, low dose subcutaneous low-molecular weight heparin or unfractionated heparin may be considered for prevention of venous thromboembolism in accord with published guidelines from the American Heart Association/American Stroke Association (AHA/ASA) and/or the European Stroke Organisation (ESO).[11,12]

- Investigational treatment(s) and/or medication(s).

5.7.3. Permitted During the Study

- Supportive care (medications and treatments) should be in alignment with the most current recommendations from the AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults in the United States and/or the ESO Guidelines for the Management of Spontaneous Intracerebral Hemorrhage.[11,12] Recommended mechanical measures for thrombo-prophylaxis should be considered. Local standard of care not in alignment with the above recommendations should be reviewed with the medical monitor on a case-by-case basis.

- Pre-study use of antiplatelet medication for an approved indication may be continued during the study at the discretion of the investigator.

5.8. Rescue Medication

There is no known specific antidote for overdose with PF-05230907. Treatment of overdose should consist of general supportive measures.

6. STUDY PROCEDURES

6.1. Screening (Up to 6.0 Hours Pre-dose)

Subjects will have completed all screening procedures as indicated to confirm they meet the eligibility criteria for the study, treatment allocation and PF-05230907 drug administration within 6.0 hours of symptom onset. The study investigator or a sub investigator will discuss, with each subject or their legally acceptable representative/legal guardian, the nature of the study, its requirements, and its restrictions.

The following procedures will be completed. Information that is in the medical record or procedures performed prior to informed consent as elements of the standard of care may be utilized to meet the respective study procedures:

- Obtain written informed consent.

- Collect subject demography: the following information should be collected; date of birth, sex, race and ethnicity. Date of birth and sex affect study eligibility and must be collected during the screening period. If the remaining demography (race and ethnicity) cannot be collected during the Screening Day 1 period, the site may collect this data as soon as possible post-dose but prior to Day 4.

- Collect medical history: the following information should be collected; GCS assessment by emergency medical services (if available), presence of chronic conditions and/or medical history of significance including history of coronary artery disease, thromboembolic disorders and ischemic disease, smoking history, and drug and non-drug allergies. The following medical history elements affect study eligibility and must be collected during the screening period:

    - Non-ICH related severe uncontrolled medical conditions, other severe acute and chronic medical and psychiatric conditions and laboratory abnormalities that may increase the risk associated with study participation.

    - Ischemic, vaso-occlusive and thrombotic events or conditions.

    - Prothrombotic disorders.

    - Thrombocytopenia.

- Coagulopathy, acute sepsis, crush injury, and disseminated intravascular coagulation events or conditions.

- Hamster protein allergies.

- If the remaining medical history elements cannot be collected during the Screening Day 1 period the site may collect this data as soon as possible post-dose but prior to Day 4.

- Collect concomitant medications: the following information should be collected; history of all known prescriptions and nonprescription drugs, and dietary and herbal supplements taken within 7 days of study enrollment. The following concomitant medication information affects study eligibility and must be collected during the screening period:

  - Oral anti-coagulant(s) (eg, warfarin or novel oral anticoagulant).

  - Low molecular-weight heparin or heparin.

  - If the remaining concomitant medication information cannot be collected during the Screening Day 1 period the site may collect this data as possible post-dose but prior to Day 4.

- Collect concomitant treatments: the following information should be collected; history of all known concomitant treatments which occurred within 7 days prior to study enrollment. If all concomitant treatments cannot be collected during the Screening Day 1 period, the site may collect this data as soon as possible post-dose but prior to Day 4.

- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).

- Complete comprehensive physical examination: physical examination should consist of assessments of general appearance, head, eyes, ears, nose and throat (HEENT), skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.

- Obtain weight: subject reported weight measured within the last 3 months is acceptable if actual weight cannot be obtained. If subject reported weight is utilized, actual weight should be collected as soon as possible post-dose.

- Obtain height: subject reported height is acceptable.

- Collect ECG: a single standard supine 12-lead ECG.

- Obtain CT scan: a CT scan is to be completed within 6.0 hours of spontaneous intracerebral hemorrhage symptom onset. Intracerebral hemorrhage diagnosis will be based on investigator interpretation of the CT scan. The CT scan will be submitted to a central vendor for final interpretation.

- Conduct ABC/2 assessment of ICH volume: investigator (or appropriately trained delegate as permitted by local, state, and institutional guidance) to complete assessment of ICH volume based on ABC/2 calculation. See Appendix 3.

    - Collect ICH characteristics (cause of ICH, location of ICH, presence of intraventricular hemorrhage [IVH], presence of edema, presence of hydrocephalus, presence of midline shift).

    - Collect results of CT angiogram (if performed as part of standard of care).

- Conduct Glasgow Coma Scale (GCS): GCS score result must be ≥6.

- Conduct retrospective mRS: mRS score result (prior to ICH onset) must be ≤3.

- Conduct the NIH Stroke Scale (NIHSS). Screening NIHSS assessment should be collected within 2 hours prior to planned treatment with PF-05230907 and as close to the time of treatment as is feasible.

- Collect the following blood samples:

    - Safety:

        - D-dimer sample collection to be processed at **local** laboratory.

        - Cardiac troponin I sample collection to be processed at local laboratory (with cardiac troponin T, where applicable) or shipped to a central laboratory.

        - Prothrombin G20210A Mutation, Factor V Leiden Mutation, tissue factor pathway inhibitor (TFPI), blood chemistry, prothrombin time/international normalized ratio (PT/INR), fibrinogen, ATIII, Protein S level, Protein C activity, and hematology (white blood cell [WBC] count, differential, hematocrit, hemoglobin, platelet) sample collections for shipment to a central laboratory. If Prothrombin G20210A and Factor V Leiden Mutation cannot be collected during the Screening Day 1 period, the site may collect as soon as possible post-dose but prior to Day 4.

    - PD sample collections (aPTT/PTT, PF1+2, and exploratory biomarker) for shipment to a central laboratory.

    - PK sample collection for shipment to a central laboratory.

- Immunogenicity sample collections (ADA, NAb, FX activity, Anti-CHO and Anti-PACE) for shipment to a central laboratory.

- Neuro-inflammation biomarker sample collection for shipment to a central laboratory.

- Banked biospecimen: Prep D1 sample collections for shipment to a central laboratory. If Prep D1 cannot be collected during the Screening Day 1 period, the site may collect the Prep D1 as soon as possible post-dose but prior to Day 4.

- Collect urine sample for urinalysis (if possible) for shipment to a central laboratory. If not feasible during the Screening Day 1 period, then sample should be collected as soon as possible post-dose.

- Obtain lower extremity Doppler Ultrasonography. If lower extremity Doppler Ultrasonography cannot be collected during the Screening Day 1 period, the site may collect this data as soon as possible post-dose; no nicotine intake should occur for approximately 1 hour prior to testing.

- Monitoring of serious adverse events.

- Review inclusion/exclusion criteria. Ensure subject meets screening entry criteria.

- Treatment allocation after eligibility is confirmed.

6.2. Study Period (Hospitalization Period)

6.2.1. Day 1 Hour 0 (Days are Relative to Start of Study Treatment)

- Conduct Glasgow Coma Scale (GCS) immediately prior to dosing.

- Drug administration:

  - The qualified administrator will administer the investigational product to subject as described in the Investigation Product Manual sent under separate cover.

6.2.2. Day 1 Hour 0 Minute 5 (±2 Minutes)

The following procedures will be completed:

- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).

- Collect the following blood samples:

  - Safety: PT/INR sample collection for shipment to a central laboratory.

- For sites in Germany, PT/INR, fibrinogen, and hematology safety labs should also be analyzed locally.

- PD sample collections (aPTT/PTT, PF1+2, and exploratory biomarker) for shipment to a central laboratory.

- PK sample collection for shipment to a central laboratory. Sample should be drawn from the opposite arm of IV infusion, and never should be drawn through the infusion catheter.

- Monitoring of serious adverse events.

- Monitoring of adverse events.

- Monitoring of concomitant medications and treatments.

6.2.3. Day 1 Hour 0 Minute 45 (±15 Minutes)

The following procedures will be completed:

- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).

- Conduct the GCS.

- Conduct the NIHSS.

- Collect the following blood samples.

  - Safety: PT/INR, fibrinogen, ATIII, Protein S level, Protein C activity and hematology (WBC count, hematocrit, hemoglobin, platelet) sample collections for shipment to a central laboratory.

    - For sites in Germany, PT/INR, fibrinogen, and hematology safety labs should also be analyzed locally.

  - PD sample collections (aPTT/PTT, PF1+2, and exploratory biomarker) for shipment to a central laboratory.

  - PK sample collection for shipment to a central laboratory.

- Monitoring of serious adverse events.

- Monitoring of adverse events.

- Monitoring of concomitant medications and treatments.

6.2.4. Day 1 Hour 3 (±30 Minutes)

- Collect the following blood samples:
    - Safety:
        - Cardiac troponin I sample collection to be processed at local laboratory or shipped to a central laboratory (with cardiac troponin T, where applicable).
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.
- If not already done, collect actual weight of study subject (as soon as possible post dose).

6.2.5. Day 1 Hour 9 (±30 Minutes)

- Collect the following blood samples:
    - Safety:
        - Cardiac troponin I sample collection to be processed at local laboratory or shipped to a central laboratory (with cardiac troponin T, where applicable).
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.

6.2.6. Day 2 (24 Hours ±6 Hours)

The following procedures will be completed:

- Complete targeted physical examination: physical examination should consist of assessments of general appearance, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.
- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).
- Collect ECG: single standard supine 12-lead ECG will be collected.

- Obtain CT scan 24 hours (±6 hours) after the baseline scan was performed: the CT scan will be submitted to a central vendor for analysis.
- Collect the following blood samples:
  - Safety:
    - Cardiac troponin I sample collection to be processed at local laboratory or shipped to a central laboratory (with cardiac troponin T, where applicable).
    - PT/INR, fibrinogen, ATIII, Protein S level, Protein C activity, and hematology (WBC count, hematocrit, hemoglobin, platelet) sample collections for shipment to a central laboratory.
      - For sites in Germany, PT/INR, fibrinogen, and hematology safety labs should also be analyzed locally.
  - PD sample collections (aPTT/PTT, PF1+2, and exploratory biomarker) for shipment to a central laboratory.
  - Neuro-inflammation biomarker sample collection for shipment to a central laboratory.
- Conduct the mRS.
- Conduct the NIHSS.
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.

6.2.7. Day 3 (48 Hours ±6 Hours)

The following procedures will be completed:

- Complete targeted physical examination: physical examination should consist of assessments of general appearance, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.
- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).

- Collect the following blood samples:
  - Safety:
    - Cardiac troponin I sample collection to be processed at local laboratory or shipped to a central laboratory (with cardiac troponin T, where applicable).
  - Neuro-inflammation biomarker sample collection for shipment to a central laboratory.
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.

6.2.8. Day 4 (72 Hours ±6 Hours)

Subjects in the study must stay in the hospital/stroke unit/ICU at a minimum through Day 4.

The following procedures will be completed:

- Complete targeted physical examination: physical examination should consist of assessments of general appearance, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.
- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).
- Collect ECG: single standard supine 12-lead ECG will be collected.
- Obtain CT or MR scan: CT or MR scan will be completed and reviewed locally for evidence of a treatment emergent ischemic event and sent to central vendor for final analysis. CT scan is the preferred imaging modality however for the Day 4 assessment a site may substitute an MR scan based on local standard of care (SoC), local regulatory, or clinical considerations at the investigator's discretion.
- Collect the following blood samples:
  - Safety:
    - D-dimer sample collection to be processed at **local** laboratory.
    - Cardiac troponin I sample collection to be processed at local laboratory (or cardiac troponin T, where applicable) or shipped to a central laboratory.

- Blood chemistry, PT/INR, fibrinogen, ATIII, Protein S level, Protein C activity, and hematology (WBC count, differential, hematocrit, hemoglobin, platelet) sample collections for shipment to a central laboratory.
    - For sites in Germany, PT/INR, fibrinogen, and hematology safety labs should also be analyzed locally.
- PD sample collection (aPTT/PTT and exploratory biomarkers) for shipment to a central laboratory.
- Neuro-inflammation biomarker sample collection for shipment to a central laboratory.

- Obtain lower extremity Doppler Ultrasonography; no nicotine intake should occur for approximately 1 hour prior to testing.
- Complete Thrombosis Clinical Probability Scores.
    - Review Wells' algorithm (Appendix 2).[15] If indicated, obtain pulmonary imaging study.
- Conduct the mRS.
- Conduct the NIHSS.
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.

If Day 4 is the date of discharge then the following additional procedures should be completed:

- Complete the comprehensive physical examination in place of targeted physical examination: physical examination should consist of assessments of general appearance, HEENT, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.
- The highest observed blood pressure result (based on systolic blood pressure) for each of the following Day 1 post-dose time intervals is to be collected: Hour 0-3, Hour 3-6, Hour 6-12, and Hour 12-24 for a total of 4 documented highest observed blood pressure (BP) results.
- Collect urine sample for urinalysis for shipment to a central laboratory.

- Collect the following blood samples:
- Immunogenicity sample collections (ADA, NAb, FX activity).
- Discuss birth control protocol specifications. This is to be documented in the subject's chart.
- Collect appropriate health resource utilization information which includes: admission date of subject to the stroke unit/ICU, discharge date of the subject from the stroke unit/ICU, admission/discharge date from the hospital (if moved from stroke unit/ICU) and as applicable, date subject began in-patient rehabilitation, and discharge date subject completed in-patient rehabilitation.
- Secure approval for release of health care information from study subject/legal guardian/legally acceptable representative as permitted by local, state, and institutional guidance to assist with collection of adverse events through Day 8 and collection of serious adverse events through Day 43.
- Telephone follow-up on Day 8 for collection of serious adverse events and adverse events since discharge.

6.2.9. Day 8 or Discharge (±24 Hours)

If the subject was discharged on Day 4 then follow directives in Section 6.2.8 and do not have subject return for a Day 8 visit. Sponsor and investigator documentation of TIEs must occur at Day 8. A telephone follow-up on Day 8 for collection of serious adverse events and adverse events since discharge will be completed if the subject is discharged prior to Day 8. If the subject was not discharged on Day 4, the following procedures will be completed on the day the subject is discharged (Day 5, Day 6, Day 7, or Day 8) or Day 8 if the subject remains in the hospital longer than Day 8:

- Complete comprehensive physical examination: physical examination should consist of assessments of general appearance, HEENT, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.
- Collect vital signs: including temperature, blood pressure, pulse rate, and respiratory rate (supine).
- The highest observed blood pressure result for each of the following Day 1 post-dose time intervals is to be collected: Hour 0-3, Hour 3-6, Hour 6-12, and Hour 12-24 for a total of 4 documented highest observed BP results (based on systolic blood pressure).
- Collect ECG: single standard supine 12-lead ECG will be collected.

- Collect the following blood samples:
  - Safety:
    - D-dimer sample collection to be processed at **local** laboratory.
  - Immunogenicity sample collections (ADA, NAb, FX activity).
- Collect urine sample for urinalysis for shipment to a central laboratory.
- Complete Thrombosis Clinical Probability Scores.
  - Review Wells' algorithm (Appendix 2).[15] If indicated, obtain lower extremity Doppler Ultrasonography and/or pulmonary imaging study; no nicotine intake should occur for approximately 1 hour prior to testing.
- Discuss birth control protocol specifications to male subjects who are able to father children and are sexually active and at risk of pregnancy-see Section 4.4. This is to be documented in the subject's chart.
- Secure approval for release of health care information from study subject/legal guardian/legally acceptable representative as permitted by local, state, and institutional guidance to assist with collection of adverse events through Day 8 (if discharged prior to Day 8) and collection of serious adverse events through Day 43.
- Monitoring of serious adverse events and adverse events. Telephone follow-up call on Day 8 for collection of serious adverse events and adverse events if subject was discharged prior to Day 8.
- Monitoring of concomitant medications and treatments.
- Collect appropriate health resource utilization information which includes: admission date of subject to the stroke unit/ICU, discharge date of the subject from the stroke unit/ICU, admission/discharge date from the hospital (if moved from stroke unit/ICU) and as applicable, date subject began in-patient rehabilitation, and discharge date subject completed in-patient rehabilitation.

6.3. Follow-up Visits

A study site should make every effort to have the subject attend the follow-up office/clinic visits, including arranging transportation if feasible (Day 43 and Day 91). If a subject is unable to attend the Day 43 and/or Day 91 study visit, or attend a scheduled remote visit on these days, a telephone follow-up for collection of serious adverse events since the last visit should occur if permitted per local, state, and institutional guidance.

6.3.1. Day 43 (±7 Days)

The following procedures will be completed:

- Collect the following blood samples:
  - Immunogenicity sample collections (ADA, NAb, FX activity, Anti-CHO and Anti-PACE) for shipment to a central laboratory.
- Conduct the mRS.
- Conduct the NIHSS.
- Document birth control utilized through the protocol required 28 days after the single dose of investigational product for male subjects who are able to father children and are sexually active and at risk of pregnancy, see Section 4.4.
- Monitoring of serious adverse events.
- Monitoring of concomitant medications and treatments.
- Collect appropriate health resource utilization information which includes: as applicable, date subject began in-patient rehabilitation, discharge date subject completed in-patient rehabilitation, date subject began out-patient rehabilitation, and discharge date subject completed out-patient rehabilitation.

6.3.2. Day 91 (±7 Days)

The following procedures will be completed:

- Collect the following blood samples **only** if subject tested positive for antibody immune response to PF-05230907 at Day 43 (sites will be notified if a subject has evidence of a previous antibody immune response to PF-05230907):
  - Immunogenicity sample collections (ADA, NAb, and FX activity) for shipment to a central laboratory.
- Conduct the mRS.
- Conduct the NIHSS.
- Collect appropriate health resource utilization information which includes: as applicable, date subject began out-patient rehabilitation, and discharge date subject completed out-patient rehabilitation.

6.4. Subject Withdrawal

Withdrawal of consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or 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 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 to contact the subject and information received during contact attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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

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

If a subject is homebound or in a rehabilitation facility and unable to attend the Day 43 and/or Day 91 visit, a study site should make every effort to assist the subject with attending an office/clinic visit (eg, arrange transportation) within the protocol window time period if at all possible as indicated in Section 6.3.1. If the subject is unable to attend a study withdrawal

visit, or is unable to attend a scheduled remote study withdrawal visit, a telephone follow-up for collection of all adverse events since the last visit should occur if permitted per local, state, and institutional guidance.

If a subject withdraws prior to Day 8/discharge, the following assessments should be completed:

- The highest observed blood pressure result (based on systolic blood pressure) for each of the following Day 1 post-dose time intervals is to be collected: Hour 0-3, Hour 3-6, Hour 6-12, and Hour 12-24 for a total of 4 documented highest observed BP results.
- Monitoring of serious adverse events.
- Monitoring of adverse events.
- Monitoring of concomitant medications and treatments.
- Collect appropriate health resource utilization information which includes: admission date of subject to the stroke unit/ICU, discharge date of the subject from the stroke unit/ICU, admission/discharge date from the hospital (if moved from stroke unit/ICU) and as applicable, date subject began in-patient rehabilitation, and discharge date subject completed in-patient rehabilitation.

If a subject withdraws after Day 8/discharge and prior to Day 43 or if antibody results at Day 43 are not yet available, the following assessments should be completed:

- Collect the following blood samples:
  - Immunogenicity sample collection (ADA, NAb, and FX activity) for shipment to a central vendor.
- Conduct the mRS.
- Conduct the NIHSS.
- Document birth control utilized through the protocol required 28 days after the single dose of investigational product for male subjects who are able to father children and are sexually active and at risk of pregnancy, see Section 4.4.
- Monitoring of concomitant medications and treatments.
- Monitoring of serious adverse events.
- Collect appropriate health resource utilization information which includes: as applicable, date subject began out-patient rehabilitation and discharge date subject completed out-patient rehabilitation.

If a subject withdraws after Day 43 and prior to Day 91, the following assessments should be completed:

- Collect the following blood samples **only** if subject tested positive for antibody immune response to PF-05230907 at Day 43 (sites will be notified if a subject has evidence of a previous antibody immune response to PF-05230907):
    - Immunogenicity sample collections (ADA, NAb, and FX activity) for shipment to a central vendor.
- Conduct the mRS.
- Conduct the NIHSS.
- Collect appropriate health resource utilization information which includes: as applicable, date subject began out-patient rehabilitation and discharge date subject completed out-patient rehabilitation.

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

7. ASSESSMENTS

Investigational sites are encouraged to explore the option for remote visits at the subject's point-of-care as an alternative mechanism to conduct the study specified visits.

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

7.1. Safety Assessments

Safety will be assessed by physical examinations, vital signs, ECGs, clinical safety laboratory results, Thrombosis Clinical Probability Scores, CT or MR scan of the brain at 72 hours, Doppler ultrasonography of the lower extremities at 72 hours (and discharge/Day 8 if applicable), and spontaneous reporting of SAEs and AEs including TIEs in all subjects who receive at least one dose of study drug.

Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians (or designees) will review individual subject data throughout the conduct of the study and the eDMC will be responsible for ongoing monitoring of study safety data (see Section 9.8).

7.1.1. Physical Examination

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. Comprehensive physical examinations and targeted physical examinations are performed at the visits specified in the Schedule of Activities. Clinically significant abnormalities that represent a change from the most recent prior observation should be considered for recording as AEs.

7.1.1.1. Comprehensive Physical Examination

A comprehensive physical examination will include the following parameters and body systems: general appearance, HEENT, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation) and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.

7.1.1.2. Targeted Physical Examination

A targeted physical examination will include the following parameters and body systems: general appearance, skin, heart (auscultation), lungs (auscultation), abdomen (palpitation and auscultation), and extremities with attention to swelling, general or localized tenderness, entire leg or calf swelling, edema, and collateral superficial veins.

7.1.1.3. Weight and Height

Actual weight should be measured in kilograms (kg). If actual weight cannot be obtained at screening, then subject reported weight from within the last 3 months may be utilized and actual weight should be collected as soon as possible post-dose. Subject reported height is acceptable.

7.1.2. Vital Signs

Vitals signs including temperature, blood pressure, pulse rate, and respiratory rate (supine) will be measured at the visits specified in the Schedule of Activities. Clinically significant abnormalities that represent a change from the most recent prior observation should be considered for recording as AEs. If during hospital confinement period, the magnitude of a vital sign abnormality is sufficient to be reported as an AE, then vital signs should be collected as a daily unscheduled observation during the hospital confinement period (eg, Day 5 through Day 8/discharge) and should be followed until the AE resolves or stabilizes (see Section 8.1).

- Body temperature should be measured by oral, tympanic, axillary or temporal method. The method chosen should be used consistently throughout the study.

- Supine blood pressure (BP) measurement should be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after 5 minutes of rest whenever possible and as permitted by the subject's medical condition. Blood pressure should not be taken from the arm with an intravenous infusion. The same arm (preferably the dominant arm) should be used throughout the study. A properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring 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.

- Respiratory rate (RR) should be measured after 5 minutes rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. The use of an automated device for measuring RR is acceptable. When blood pressure is to be taken at the same time, respiration measurement should start after 5 minutes of rest and before blood pressure measurement.

7.1.2.1. Highest Observed Blood Pressure Documentation

The highest observed blood pressure (systolic pressure) result reflected in the hospital record/source documents will be recorded for the time-intervals specified in the Schedule of Activities.

7.1.3. ECG

A single standard supine 12-lead ECG should be performed after the subject has rested quietly for at least 10 minutes in a supine position at times specified in the Schedule of Activities. Clinically significant abnormalities that represent a change from the Day 1 screening/baseline visit should be considered for recording as AEs and evaluated further as clinically warranted.

The Day 1 screening ECG values will serve as each subject's baseline values. When the timing of the measurements coincides with a blood collection, the ECG should be obtained prior to the nominal time of the blood collection. To ensure safety of the subjects, a qualified individual (eg, investigator, sub-investigator) at the study site will make comparisons to baseline measurements. A paper or digital copy of the ECG should be filed in the subjects chart and must be available to the sponsor upon request.

If a scheduled single ECG assessment reveals a clinically significant abnormality (other than the Day 1 screening value) then 2 additional ECGs should be collected to confirm the original observation.

7.1.4. Thrombosis Clinical Probability Scores

Thrombosis clinical probability scores consist of two assessments, the Simplified Clinical Model for Assessment of deep vein thrombosis (DVT) and Variables Used to Determine Patient Pretest Probability for Pulmonary Embolism (PE). These assessments are used to

categorize subjects as having low, moderate or high probability of having a DVT or PE respectfully. A physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation will complete each assessment by reviewing the clinical variables and indicating the corresponding score. These scores are totaled and compared with the coordinating probability score located in the footnote of each assessment scale.

The Probability Scores will be completed and calculated at times specified in the Schedule of Activities. Sites should refer to Well's publication "Integrated strategies for the diagnosis of venous thromboembolism" for additional guidance regarding recommended post treatment evaluation for possible deep vein thrombosis and/or pulmonary embolism, which may require additional Doppler lower extremity ultrasonography.[15]

7.1.5. Doppler Lower Extremity Ultrasonography

A Doppler lower extremity ultrasonography will be completed at the time specified in the Schedule of Activities. In the event of abnormal Doppler lower extremity ultrasonography result, the investigator should initiate treatment and/or additional diagnostic studies as clinically warranted. No nicotine intake should occur for approximately 1 hour prior to testing.

7.1.6. Cardiac Troponin I

Serial results of cardiac troponin I should be followed in conjunction with other correlated parameters including ECG in order to assess for the possibility of acute evolving or recent MI based on criteria from Myocardial infarction redefined – A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction.[20] For safety analyses the central laboratory results for cardiac troponin I will take precedence over local determinations for cardiac troponin T.

7.1.7. CT or MR Scan at Day 4 (72 Hours Post-dose)

A CT or MR scan will be completed as indicated in the Schedule of Activities and reviewed locally by a qualified physician for evidence of a treatment emergent ischemic event at Day 4 (72 hours post-dose). CT scan is the preferred imaging modality however for the Day 4 assessment a site may substitute an MR scan based on local standard of care (SoC), local regulatory, or clinical considerations at the investigator's discretion. Clinically significant results that represent changes from the Day 2 (24 hour post-dose) imaging should be considered for recording as AEs or SAEs per protocol Section 8. The scan will be sent to central vendor for final analysis.

7.1.8. TIEs Through Day 8

TIEs (Appendix 1) are to be reported by the study site following protocol Section 8.6.1 and Section 8.14. The dose toxicity relationship for each cohort is based upon the TIE data and is reviewed as part of the mCRM design, therefore it is essential these events be reported as AEs or SAEs in a timely manner by the study site.

7.1.9. Clinical Laboratory Tests

Blood and urine samples will be collected at the time specified in the Schedule of Activities. Protocol required testing includes Prothrombin G20210A Mutation, Factor V Leiden Mutation, TFPI, **D-dimer (local laboratory),** blood chemistry, PT/INR, Fibrinogen, ATIII, Protein S level, Protein C activity, hematology, cardiac troponin I, and urinalysis. All tests will be shipped to the central laboratory unless otherwise noted. For sites in Germany, PT/INR, fibrinogen, and hematology labs collected after Day 1, Hour 0 (post-dose) should also be analyzed locally.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the central laboratory manual prior to initiation of the trial. Unscheduled clinical laboratory testing may be obtained at any time during the study to assess any perceived safety concerns. Clinically significant abnormal findings that represent changes from the most recent prior assessment should be recorded as AEs per Section 8.5 and Section 8.6.1.

7.2. Immunogenicity

7.2.1. Plasma for Analysis of ADA (Anti-PF-05230907) and NAb

During all study periods, blood samples will be collected at times specified in the Schedule of Activities. Samples will be tested for ADA using a tiered strategy of screen, confirm specificity, and characterize titer. ADA positive samples will further be characterized for cross reactivity to native FX, cross reactivity to native FXa, and NAb.

- Anti-PF-05230907 antibody samples will be analyzed using a validated bridging electrochemiluminescent assay in compliance with Pfizer standard operating procedures. Cross reactivity to native FX and FXa will be assessed using additional confirmatory tiers in the anti-PF-05230907 antibody assay.

- Neutralizing anti-PF-05230907 antibody samples will be analyzed using a partially validated chromogenic bioassay in compliance with Pfizer standard operating procedures as applicable.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

- The immunogenicity samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the immunogenicity processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

- As part of understanding the immunogenicity of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.2.2. Plasma for Analysis of FX Activity

During all study periods, blood samples will be collected at times specified in the Schedule of Activities.

Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

7.2.3. Plasma for Analysis of Anti-Chinese Hamster Ovary (CHO) Protein and anti-PACE (furin) Antibodies

During all study periods, blood will be collected at times specified in the Schedule of Activities. Samples will be tested in each assay using a tiered strategy of screen, confirm specificity, and titer characterization.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

- Anti-CHO protein antibodies and anti-PACE antibodies will be assessed using direct enzyme-linked immunosorbent assays (ELISAs) validated in compliance with Pfizer standard operating procedures.

7.3. Pharmacodynamics

Blood samples will be collected at the time specified in the Schedule of Activities. Protocol required testing includes aPTT/PTT and PF1+2. Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

The pharmacodynamic (PD) samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PD processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of understanding the pharmacodynamics of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report.

7.4. Pharmacokinetics

Blood samples will be collected at times specified in the Schedule of Activities.

The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60 minute sample) from dosing or ±2 minute for samples less than 10 minutes from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF).

Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

- Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

- As part of understanding the pharmacokinetics of the study drug, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. This data will be used for internal exploratory purposes and will not be included in the clinical study report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.5. Exploratory Biomarkers

Some of the planned biomarker(s) may not be performed if not supported by data from the ongoing pre-clinical work.

7.5.1. PD Biomarkers

Blood samples for exploratory biomarkers that may reflect pharmacologic effect of PF-05230907 or ICH progression will be collected at the time specified in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

7.5.2. Neuro-inflammation Biomarkers

Blood samples for neuro-inflammation and/or neurological outcomes to better understand ICH will be collected at the time specified in the Schedule of Activities. Details regarding the collection, processing, storage and shipping of the blood samples will be provided to the investigator site in the study laboratory manual prior to initiation of the trial.

7.6. Pharmacogenomics

7.6.1. Banked Biospecimens

7.6.1.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomics/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomics/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by swiping a badge. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will be used only for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians, nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

A 4-mL blood biospecimen **Prep D1 (K_2 edetic acid [ethylenediaminetetraacetic acid] [EDTA] whole blood collection optimized for DNA analysis)** will be collected per the Schedule of Activities to be retained for potential pharmacogenomics/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug-metabolizing enzyme genes, drug-transport protein genes, or genes thought to be related to the mechanism of drug action may be examined.

The banked biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.6.2. Additional Research

Unless prohibited by local regulations or ethics committee decision, subjects will be asked to indicate on the consent form whether they will allow the banked biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical study, and related conditions;
- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation among people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in the Markers of Drug Response section will be used. Subjects may still participate in the clinical study if they elect not to allow their banked biospecimens to be used for the additional purposes described in this section.

7.7. Diagnostic Assessments

7.7.1. Brain CT Scan

A diagnostic brain CT scan is to be completed within 6.0 hours from subject's symptom onset. The CT scan completed within 6.0 hours from subject's symptom onset is to be assessed by a qualified physician at the investigator site for purposes of determining study eligibility and to provide a baseline assessment of ICH volume (by ABC/2 method, see Section 4.6.1). The CT scan will be sent to the central vendor for final analysis.

An imaging procedure manual will be provided to the Investigator site prior to initiation of the trial. CT angiography data will be collected if performed as part of the standard of care.

7.7.1.1. ABC/2 Assessment of ICH Volume

The ABC/2 is to be completed within 6.0 hours from subject's symptom onset and prior to enrollment in the study by a qualified physician at the investigator site (see Section 4.6.1).

7.8. Triggered Requirements

Condition	Action
Subjects with previous evidence of an antibody immune response to PF-05230907 at Day 43 (sites will be notified if a subject has evidence of a previous antibody immune response to PF-05230907 as defined in Section 9.6.1).	Collect immunogencity blood samples (ADA, Nab, and FX activity) at Day 91 for shipment to a central vendor.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

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

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 42 calendar days post-dose (Day 43) after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

SAEs should be recorded on the case report form (CRF) from the time the subject has signed the informed consent document through 42 days post-dose (Day 43).

AEs should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through 7 days post-dose (Day 8).

8.3. Definition of an Adverse Event

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

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

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

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

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, at the wrong dosage strength, or the administration of investigational product that has undergone temperature excursion from the

specified storage range as indicated in the Investigational Product Manual, unless it is determined by the sponsor that the investigational product under question is acceptable for use. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

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

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

The Investigational Product Manual provides criteria for departures from the actual protocol specified dose that will be considered medication errors.

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

8.5. Abnormal Test Findings

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

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

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

8.6. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);

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

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

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Medical Device Complaint Reporting Requirements). 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.

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between the investigational product and an event specified below, these events should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section of this protocol. These events are anticipated to occur commonly in a population with intracerebral hemorrhage. However, these events should still be captured as AEs in the CRF.

Protocol-specified events that will not normally be reported in an expedited manner:

1. Disseminated intravascular coagulation.
2. Acute coronary syndrome.
3. Cardiac arrest.
4. Myocardial infarction.
5. Cardiac troponin I increased.
6. Ischemic stroke.
7. Transient ischemic attacks.
8. Purpura.
9. Superior vena cava syndrome.
10. Thromboembolic event.
11. Visceral arterial ischemia.
12. Peripheral arterial ischemia.
13. Hospitalization due to ICH.
14. DVT.
15. Hemorrhagic stroke.
16. Arterial ischemic events.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

8.6.2. Potential Cases of Drug-Induced Liver Injury

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

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

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

    Concurrent with

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

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

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

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

Severity of adverse events will be graded based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guidance:

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

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.

8.9. Causality Assessment

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

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

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

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

   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).

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.11. Occupational Exposure

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

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

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

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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 event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

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

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

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

8.14.2. Nonserious Adverse Event Reporting Requirements

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

8.14.3. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected 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 have led 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. Sites should contact their study monitor (or equivalent).

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Summary statistics and listings will be used to analyze the study data. Summary of demographic and baseline characteristics, safety (including immunogenicity), efficacy and PK/PD data will be conducted by dose group (and overall if appropriate).

9.1. Statistical Methods

A general description of the original continual reassessment method (CRM) design and its various modified CRM (mCRM) designs can be found in a tutorial paper by Garrett-Mayer.[13] This study employs a mCRM design similar to Goodman et al. to estimate the MTD.[14] In this study, the mCRM design utilizes Bayesian methodology to learn the dose-toxicity relationship continuously after each cohort's thromboembolic and/or ischemic event (TIE) data becomes available. The underlying dose-TIE relationship is assumed to follow a one-parameter hyperbolic-tangent model.

$$f(x, \beta) = [\frac{1 + \tanh(x)}{2}]^{\beta},$$

where x is an adjusted dose which could be computed from an initiate dose-toxicity curve, β is an unknown parameter with a prior distribution pre-specified at the beginning of the trial, and tanh is the hyperbolic-tangent function.

The dose grid for the mCRM design is specified in Table 2. The starting dose is 5 μg/kg, but lower doses are included in the dose grid to allow step-down option if a high TIE rate occurs in the first cohort assigned to 5 μg/kg by chance. A prior uniform distribution, Unif [0,3], placed on the model parameter β and the vector of estimated probability of TIE when β=1, shown in Table 3, define the "starting point" of the mCRM algorithm. Based on clinical input, this initial dose-TIE profile assumes that a TIE rate of 15% can occur as early as 8-10 μg/kg and further increases to 27% and 49% at 15 μg/kg and 37 μg/kg, respectively. The estimated TIE rates for other doses were imputed based on the projected initial dose-TIE curve. The adjusted doses (ie, x in the hyperbolic-tangent model) were computed from the hyperbolic tangent model by setting β=1.

Table 3. Estimated Probability of TIE when β=1

Dose (μg/kg)	Estimated TIE Rate	Adjusted Dose (x)
1	2.5%	-1.83
2	3.3%	-1.69
3	4.5%	-1.53
4	6%	-1.38
5*	8%	-1.22
6	10.5%	-1.07
8	13.5%	-0.93
10	17.5%	-0.78
12	22%	-0.63
15	27%	-0.50
19	32.5%	-0.37
24	38%	-0.24
30	43%	-0.14
37	49%	-0.02
47	55%	0.10

* starting dose

After the TIE data from the first cohort (5 μg/kg) becomes available, the prior distribution of β will be updated into a posterior distribution through Bayesian Markov Chain Monte Carlo (MCMC) simulations in adaptive design explorer (ADE). The model-based MTD will be estimated as $f^{-1}(0.15, \hat{\beta})$, where 0.15 is the pre-specified target TIE rate at MTD and $\hat{\beta}$ is the posterior mean of β. The next cohort of 3 subjects will be dosed at the dose level closest to this estimated MTD but not exceeding it, subject to additional pre-specified dose escalation constraints and clinical oversight. The posterior distribution of β will become the prior distribution in the next round of updates. The details of Bayesian analyses will be documented in the statistical analysis plan. This process is continued until at least one of the following stopping rules is met:

1. Maximum sample size of 51 subjects has been reached.

2. MTD has been identified with sufficient accuracy, ie, 12 subjects have been accumulated on a dose that is currently estimated to be the MTD.

3. All doses appear to be overly toxic and MTD cannot be determined in the current trial setting.

Starting from the second cohort and until the end of the trial, the above described mCRM algorithm constantly incorporates additional information about dose-TIE relationship learned from the data via modeling and that is reflected on the projected MTD. By design, such dose allocation procedure will eventually cluster dose assignments around the dose yielding an approximately 15% TIE rate.

Like all Bayesian methods, the adopted mCRM design may be sensitive to prior information placed on the model parameter β at the beginning of the trial. However, as the trial progresses and the DLT data accumulates, it eventually overrules the prior information and latter becomes less important.

9.2. Simulations for mCRM Design

Extensive simulations were performed to compare the operating characteristics of various competing mCRM designs in order to fine-tune mCRM performance and choose the 'best' mCRM design. Below is a brief description of the simulation setup and key findings. All the simulations were performed in ADE (v3.0.2.1).

Different combinations of cohort sizes (2 or 3), maximum dose escalation allowed between cohorts (1, 2 or 3 doses), stopping rules (maximum number of 6, 9, 12, 15, 18 and 24 subjects on MTD), mCRM dose-toxicity model (power or hyperbolic-tangent), and starting dose (5 μg/kg or 8 μg/kg) were examined. Competing designs were evaluated under 6 different plausible scenarios of dose-TIE curves varying in steepness, location of the true MTD and overall toxicity level in the range of the dosing grid.

For each of the above competing designs, the operating characteristics were compared by scenario to evaluate the trade-off between precision of MTD estimation and study efficiency. The final chosen design is a mCRM design with cohort size of 3, a starting dose of 5 μg/kg, and the stopping rule with maximum 12 subjects on MTD using the hyperbolic-tangent dose-toxicity working model. Based on simulations, this design provides, on average, a more accurate estimate of MTD and comparable or less proportion of subjects receiving doses higher than the MTD than the conventional 3+3 design, with an acceptable increase in the average sample size. Details of the simulations were documented in a simulation report for this study.

9.3. Sample Size Determination

No formal sample size calculation is performed. The minimum sample size of the study is approximately 20. The maximum study sample size is set as 51 in order to have a reasonable chance to identify the correct MTD based on statistical simulations. The actual sample size of the study will depend on the underlying dose-TIE relationship and variability in the actual data realization. The cohort size is 3. If the study stops with a MTD declared and the maximum sample size has not been reached, 12 subjects must have been studied at the MTD dose. The actual number of subjects at each dose will vary.

9.4. Efficacy Analysis

All study efficacy endpoints, including hemostatic endpoints (ICH absolute and percent change from baseline volume) and neurological outcomes (mRS and NIHSS) are exploratory endpoints.

CCI [redacted] If appropriate, a mixed-effects model for repeated measure will also be utilized to summary the hemostatic endpoints with fixed effects of dose group, CT scan time and dose group by CT scan time interaction and an appropriate covariance matrix for repeated measurements. Point estimates and confidence intervals of the hemostatic endpoints for each dose group will be produced by CT scan time.

9.5. Analysis of Other Endpoints

9.5.1. Pharmacokinetic Analysis

PF-05230907 concentration in plasma is an exploratory endpoint. Available plasma concentration of PF-05230907 will be descriptively summarized and plotted by nominal PK sampling time and dose group. Due to the short half-life ($t_{½}$) and limited sampling, noncompartmental parameters will not be calculated for the study report.

9.5.2. Pharmacodynamics Analysis

The pharmacodynamic endpoints include aPTT or PTT and PF1+2, within 2 days of dosing. These will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

9.6. Safety Analysis

All subjects who received the treatment of PF-05230907 will be included for safety analysis.

Safety endpoints, including treatment emergent TIEs, treatment emergent serious adverse events, treatment emergent adverse events, treatment emergent laboratory abnormality, physician examination changes, vital signs changes, ECG results and other safety data will be summarized descriptive by dose group. Listings and/or graphic displays will also be generated, where appropriate. As discussed in Section 9.1, the TIE data from the current cohort will be utilized for the mCRM design along with clinical and eDMC oversight to determine the dose for the next cohort.

9.6.1. Immunogenicity Analysis

ADA, NAb and Factor X activity level will be summarized by dose and time points for samples tested. Subjects with ADA and NAb immune responses will be summarized by dose. An ADA immune response following study drug administration is defined as:

- A confirmed post-treatment positive assay result in combination with a negative baseline sample assay result; or
- A confirmed post-treatment positive assay result in combination with at least one dilution factor increase in titer relative to a positive baseline sample assay result.

Positive ADA responses to PF-05230907 will be further confirmed for cross reactivity against native FX and native FXa. Positive ADA responses will also be evaluated for neutralizing antibody immune response against PF-05230907. Neutralizing antibody immune responses will be assessed by results from a neutralizing assay and/or from the factor X activity assay. A subject with neutralizing antibody immune response is defined as either:

- A positive result from at least one sample tested in the neutralizing assay; or

- Depletion of study subject factor X activity (>50% reduction relative to baseline) in the basal state, at assessments subsequent to study drug administration in combination with a demonstrated positive ADA immune response and in the absence of any other plausible explanation for decline in factor X activity.

In the presence of ADA to PF-05230907 that is cross reactive with native FX or native FXa, a positive neutralizing antibody response against PF-05230907 will be imputed to be cross reactive against native FX or native FXa respectively.

9.7. Interim Analysis

There are no formal statistical interim analyses. For the determination of the dose for the next cohort, analyses of all available TIE data will be performed after TIE data becomes available for the current cohort. Observed TIE data will be used to update the dose-toxicity model, which will recommend a dose for the next cohort of subjects. Other safety biomarker data from the trial will also be taken into consideration to provide clinical oversight in determining the dose for the next cohort. Study will be stopped if at least one of the stopping criteria described in Section 9.1 has been met.

9.8. Data Monitoring Committee

This study will use an external data monitoring committee (eDMC). The eDMC will be responsible for ongoing cumulative reviews of the study safety data. The eDMC chair (or designee) will also be required to review an interim review memo including all 7-day safety data for each completed cohort, in order to provide authorization to proceed with enrollment. At his/her discretion, the eDMC chair may direct that dosing at the respective dose level (or higher dose levels) be paused until a full meeting of the eDMC has been convened. In addition, if a SUSAR or 2 or more grade 3 or higher adverse events that are considered at least possibly related to treatment with PF-05230907 are observed in the initial cohort evaluating a dose level that exceeds previously investigated dose levels, dosing at the respective dose level (or higher dose level) will be paused and the eDMC will be convened. These eDMC requirements will also be specified in the eDMC charter. Review of efficacy data will not be a responsibility of this committee. The recommendations made by the eDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions to regulatory authorities as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

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

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

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

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

The only circumstance in which an amendment may be initiated prior to IRB/EC/CA 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/CA and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

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

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

12.3. Subject Information and Consent

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

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

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

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

Adult subjects with ICH will present in acute care settings (eg, emergency room, ICU), may be decisionally impaired and may be unable to provide written informed consent. Due to the life-threatening and severely disabling nature of ICH and the lack of effective treatment for ICH, treatment with PF-05230907 may have the potential for benefit in this vulnerable population. Based on local regulations and institutional policies, the respective study investigators will determine if consent may be obtained from a subject's legally acceptable representative or legal guardian. Whenever consent is obtained from a subject's legally acceptable representative or legal guardian and the investigator determines the subject has regained the capacity to provide consent, the subject's consent is to be obtained.

The investigator must ensure that each study subject or his or her legally acceptable representative or legal guardian, 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 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.

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

12.4. Subject Recruitment

Subject recruitment efforts are not required for this study because this study will be conducted in an acute condition (ICH) with rapid onset which generally is not by definition diagnosed until subjects are at the study site.

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

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

End of trial in all 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-05230907 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 2-4 weeks. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

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

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

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

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

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

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

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

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Appendix 1. Thromboembolic and Ischemic Events (TIEs) and Associated Severity Grade (CTCAE V4.03 Scale) for Determination of MTD[10]

Adverse Event	Grade Defining a TIE	Grade and Description
Disseminated intravascular coagulation	3 or higher	1: Not defined 2: Laboratory findings with no bleeding 3: Laboratory findings and bleeding 4: Life-threatening consequences; urgent intervention indicated 5: Death
Acute coronary syndrome	3 or higher	1: Not defined 2: Symptomatic, progressive angina; cardiac enzymes normal, hemodynamically stable 3: Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable 4: Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable 5: Death

Adverse Event	Grade Defining a TIE	Grade and Description
Cardiac arrest	4 or higher	1: Not defined 2: Not defined 3: Not defined 4: Life threatening consequences; urgent intervention indicated 5: Death
Myocardial infarction	3 or higher	1: Not defined 2: Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes 3: Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction 4: Life-threatening consequences; hemodynamically unstable 5: Death

Adverse Event	Grade Defining a TIE	Grade and Description
Cardiac troponin I increased	3	1: Levels above the upper limit of normal and below the level of myocardial infraction as defined by the manufacturer 2: Not defined 3: Levels consistent with myocardial infarction as defined by the manufacturer 4: Not defined 5: Not defined
Ischemia cerebrovascular	1 or higher and associated with lesion(s) on CT/MRI not contiguous with the ICH lesion and in a discrete separate area of the brain	1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated 2: Moderate symptoms 3: Not defined 4: Not defined 5: Not defined

Adverse Event	Grade Defining a TIE	Grade and Description
Portal vein thrombosis	2 or higher	1: Not defined 2: Intervention not indicated 3: Medical intervention indicated 4: Life-threatening consequences; urgent intervention indicated 5: Death
Ischemic stroke based upon CTCAE V4.03 toxicity criteria for stroke	1 or higher and associated with lesion(s) on CT/MRI not contiguous with the ICH lesion and in a discrete separate area of the brain	1: Asymptomatic or mild neurologic deficit; radiographic findings only 2: Moderate neurologic deficit 3: Severe neurologic deficit 4: Life-threatening consequences; urgent intervention indicated 5: Death

Adverse Event	Grade Defining a TIE	Grade and Description
Transient Ischemic attacks	2	1: Mild neurological deficit with or without imaging confirmation 2: Moderate neurologic deficit with or without imaging confirmation 3: Not defined 4: Not defined 5: Not defined
Purpura	2 or higher	1: Combined area of lesions covering <10% BSA 2: Combined areas of lesions covering 10-30% BSA; bleeding with trauma 3: Combined areas of lesions covering >30% BSA; spontaneous bleeding 4: Not defined 5: Not defined

Adverse Event	Grade Defining a TIE	Grade and Description
Superior vena cava syndrome	1 or higher	1. Asymptomatic; incidental finding of SVC thrombosis 2. Symptomatic; medical intervention indicated (eg, anticoagulation, radiation, or chemotherapy) 3: Severe symptoms; multi-modality intervention indicated (eg, anticoagulation, chemotherapy, radiation, stenting) 4: Life-threatening consequences; urgent multi-modality intervention indicated (eg, lysis, thrombectomy, surgery) 5: Death
Thromboembolic event	2 or higher	1: Venous thrombosis (eg, superficial thrombosis) 2: Venous thrombosis (eg, uncomplicated deep vein thrombosis), medical intervention indicated 3: Thrombosis (eg, uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombosis), medical intervention indicated 4: Life-threatening (eg, pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated 5: Death

Adverse Event	Grade Defining a TIE	Grade and Description
Visceral arterial ischemia	2 or higher	1: Not defined 2: Brief (<24 hours)episode of ischemia managed medically and without permanent deficit 3: Prolonged (>=24 hours) or recurring symptoms and/or invasive intervention indicated 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated 5: Death
Peripheral arterial ischemia	3 or higher	1: Not defined 2: Brief (<24 hrs) episode of ischemia managed medically and without deficit 3: Prolonged (>=24 hours) or recurring symptoms and/or invasive intervention indicated 4: Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated 5: Death

Appendix 2. Thrombosis Clinical Probability Scores[15]

Simplified Clinical Model for Assessment of DVT*	
Clinical variable	**Score**
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2

DVT, deep vein thrombosis. *≥2, probability of DVT is 'likely'. ≤1, probability for DVT is 'unlikely'. Alternatively, <1 is low probability, moderate is 1 or 2, and high is >2.

Variables Used to Determine Patient Pretest Probability for Pulmonary Embolism*	
Clinical variable	**Score**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpitation of the deep veins)	3
PE as or more likely than an alternative diagnosis	3
Heart rate greater than 100	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 month or palliative)	1

DVT, deep vein thrombosis; PE, pulmonary embolism. *>4, probability of PE is 'likely'. ≤4, probability for PE is 'unlikely'. Alternatively, <2 is low probability, moderate is 2-6, and high is >6.

Appendix 3. ABC/2[16]

ABC/2 formula: A is the greatest hemorrhage diameter by CT, B is the diameter 90° to A, and C is the approximate number of CT slides with hemorrhage multiplied by the slide thickness.

The derivation of the ABC/2 formula is as follows: The volume of an ellipsoid is $4/3\pi(\boldsymbol{A}/2)(\boldsymbol{B}/2)(\boldsymbol{C}/2)$, where ***A***, ***B***, and ***C*** are the three diameters. If π is estimated to be 3, then the volume of an ellipsoid becomes $\boldsymbol{ABC}/2$.

Appendix 4. National Institute of Health Stroke Scale[17]

Online certification and reference for the NIHSS can be found at https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=nihss-english.trainingcampus.net

A copy of the NIHSS assessment forms will be supplied to the site with the B2341002 study documentation.

Summary of the assessment from http://www.nihstrokescale.org/ is detailed below:

The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The single patient assessment requires less than 10 minutes to complete.

The evaluation of stroke severity depends upon the ability of the observer to accurately and consistently assess the patient.

Appendix 5. Glasgow Coma Scale[18]

Component	Rating	Score
Eyes Open	Spontaneous	4
	To sound	3
	To pressure	2
	None	1
Verbal Response	Oriented	5
	Confused	4
	Words	3
	Sounds	2
	None	1
Motor Response	Obeys commands	6
	Localising	5
	Normal flexion	4
	Abnormal flexion	3
	Extension	2
	None	1

Appendix 6. Modified Rankin Scale (mRS)[19]

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

The following link should be used to access the training module for the mRS:

https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=rankin-english.trainingcampus.net

Appendix 7. Abbreviations

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

Abbreviation	Term
ADA	anti-drug antibody
ADE	adaptive design explorer
AE	adverse event
AHA/ASA	American Heart Association/American Stroke Association
ALT	alanine aminotransferase
Anti-CHO	anti-Chinese hamster ovary
Anti-PACE	anti-paired basic amino acid cleaving enzyme
APC	activated protein C
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATIII	antithrombin III
BID	twice daily
BP	blood pressure
CA	Competent Authority
CDS	core data sheet
CRF	case report form
CRM	continual reassessment method
CSA	clinical study agreement
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CT	computed tomography
CV	coefficient of variation
DNA	deoxyribonucleic acid
DU	dispensable unit
DVT	deep vein thrombosis
EC	effective concentration
EC	ethics committee
ECG	electrocardiogram
ED	effective dose
eDMC	external data monitoring committee
EDP	exposure during pregnancy
EDTA	edetic acid (ethylenediaminetetraacetic acid)
ELISAs	Enzyme-linked immunosorbent assays
EMS	emergency medical services
ESO	European Stroke Organisation
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)

Abbreviation	Term
FIH	first in human
FSH	follicle-stimulating hormone
FVa	factor Va
FX	factor X
GCP	good clinical practice
GCS	Glasgow coma scale
GLP	good laboratory practice
HEENT	head, eyes, ears, nose and throat
IB	investigator's brochure
ICH	intracerebral hemorrhage
ICH	International Conference on Harmonisation
ICU	intensive care unit
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IVH	intraventricular hemorrhage
IVR	interactive voice response
IWR	interactive web response
kg	kilogram
LFT	liver function test
LMWH	low molecular-weight heparin
LRP	lipoprotein receptor-related protein
LSLV	last subject last visit
MCMC	Markov Chain Monte Carlo
mCRM	modified continual reassessment method
MED	minimum effective dose
MR or MRI	magnetic resonance imaging
mRS	modified Rankin score
MTD	maximum tolerated dose
NAb	neutralizing antibody
N/A	not applicable
NCI	National Cancer Institute
NIHSS	National Institute of Health Stroke Scale
NOAL	no observed effects level
NOAEL	no observed adverse effect level
OBU	Oncology Business Unit
PD	pharmacodynamic
PE	pulmonary embolism

Abbreviation	Term
PF1+2	prothrombin fragment 1+2
PK	pharmacokinetic
PT	prothrombin time
PWRD	Pfizer Worldwide Research and Development
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SCL	Supply Chain Lead
SoA	schedule of activities
SOP	standard operating procedure
SPC	summary of product characteristics
SRSD	single reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAT	thrombin-antithrombin
TEAE	treatment emergent adverse event
TIE	thromboembolic and/or ischemic event
TFPI	tissue factor pathway inhibitor
TX	toxicokinetics
VISTA	virtual international stroke trial archive
WBC	white blood cell
ULN	upper limit of normal
US	United States
USPI	United States package insert

Appendix 8. Definition for Subjects Capable of Providing Consent in Sweden

Enrollment of subjects in Sweden is limited to individuals who are able to provide their personal informed consent. Individuals conscious, oriented and able to follow commands are considered able to provide their own consent and in Sweden these individuals are operationally defined by the following criteria:

Inclusion Criteria

- Glasgow Coma Scale score ≥14.

Exclusion Criteria

- Individuals with aphasia (verbal Glasgow Coma Scale score <5 and NIH Stroke Scale Score >0 in item 9).
- Individuals with dementia.
- Individuals with a reduced level of consciousness (NIH Stroke Scale score ≥1 in item 1).