Protocol B2341002

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)

Statistical Analysis Plan (SAP)

Version: Amendment 1

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NOTE: *Italicized* text within this document has been taken verbatim from the Protocol.

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1. VERSION HISTORY

The first version of the Statistical Analysis Plan (SAP) for study B2341002 was based on the protocol amendment 1 dated 28 June 2016. This SAP amendment reflects changes made to the protocol to ensure that the analyses described are consistent with those described in the study protocol amendment 2 dated 17 January 2017.

Pfizer made the decision to terminate the study early after 21 subjects were enrolled in the study in October 2017. Changes in the analyses plan reflect this early study termination.

Table 1. Summary of Major Changes in SAP Amendments

Version: SAP amendment 1	
Summary of Changes	**Rationale**
• Removed the requirement for AEs to be in the same system organ class from the criteria for sequential dosing and ad hoc eDMC meetings. • 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. • Added a statement on the precedence of centrally-analyzed troponin I, versus locally analyzed troponin T, for safety data review purposes.	This was required by regulatory authorities in Germany and was reflected in protocol amendment 2.
Added "based on available data during the safety review period after each respective cohort completes dosing." Section 6.1.1.1. and minor edits on Section 7.4.2.	Clarification of the mCRM analyses and safety review procedure conducted between Cohorts.
Added a footnote to Table 4	Clarification of the extended visit window for discharge day other than Day 8.
• Removed subset analyses (Section 6.4), wordings referring to Kaplan-Meier analyses, mixed effects model for repeated measures, analyses of CT parameters and exploratory efficacy endpoints NIHSS and mRS, sliding dichotomy and ordinal analyses of mRS. • Simplified graphical presentation and analyses of	Early study termination: Limitation of sample size and the business decision of not to progress to Phase 2 efficacy study for ICH diminished the utility of the original proposed analyses.

various exploratory measures in Section 6.3 and Section 6.7.	

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B2341002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study 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. 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, dose escalation will be conducted in a limited number of subjects per cohort (N=3). Sequential dosing criteria will be assessed for each cohort, dosing will be paused following completion of each cohort, internal safety monitoring and external Data Monitoring Committee (eDMC) review of the safety data will be conducted. *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 determination of MTD using mCRM dose-toxicity modeling will be based on TIEs which occur through 7 days post-dose (Day 8). *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. Subjects will be enrolled in cohorts of 3, starting with an initial dose of 5 μg/kg for the first cohort. 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.*

To avoid an overly aggressive dose escalation scheme (especially early in the trial when limited TIE data is available), 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 (Table 2), which results in a 50-67% increase in dose from the 5 μg/kg dose. Four doses (1-4 μg/kg) lower than the starting dose are included in the dose grid to allow dose de-escalation if a high TIE rate occurs in the first cohort assigned to 5μg/kg. In addition, Pfizer might modify the dose level assignment for the next cohort from the model-based estimate to a more conservative dose level based upon clinical oversight or external Data Monitoring Committee (eDMC) recommendations.

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.

2.2.1. **Sample Size**

No formal sample size calculation is performed. The minimum and maximum sample sizes of the study are 20 and 51, respectively. For a cohort size of 3, the maximum study sample size is set as 51 (17 cohorts) 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. 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 number of subjects treated at each dose and a particular dose-assignment sequence 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.

2.2.2. **Enrollment Pause**

As safeguards for subject safety, an enrollment pause can occur within a cohort of 3 subjects, and will occur after each cohort completes dosing.

2.2.2.1. **Sequential dosing**

Sequential dosing of subjects in a cohort meeting one of the following criteria will be implemented:

1. The initial cohort evaluating a dose level that exceeds previously administered dose levels.
2. The subsequent (second) cohort evaluating the respective dose level at which 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.

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.

2.2.2.2. **Progression to subsequent cohort**

An enrollment pause will occur after each respective cohort completes dosing. Progression to each subsequent cohort of study subjects will not occur until the following are completed:

1. Sponsor review of the available safety data through Day 8 (or discharge) post-dose administration.
2. Discussion with the investigator(s)/sub-investigator(s) for each subject in the respective cohort.
3. An interim review memo including all specified 7-day safety data has been provided to the eDMC chair (or designee).
4. The mCRM-determined dose recommendation and any adjustment of mCRM-determined dose to more conservative dose levels when deemed appropriate by the sponsor or eDMC is attained.
5. An authorization has been received from the eDMC chair to proceed with enrollment of the subsequent cohort.

2.2.2.3. **eDMC Review of Cohort Safety Data**

The eDMC will be responsible for ongoing cumulative reviews of the study safety data. If there is a safety concern after safety data review, 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. The recommendations made by the eDMC to alter the conduct of the study will be forwarded to Pfizer for final decision.

2.2.3. **Safety Biomarker Criteria for Dose Escalation Adjustment**

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 leading to a maximum of 67% increase in dose for the 5 μg/kg dose and above. This feature is incorporated into the study design module of the mCRM algorithm for dose recommendation.

Dose increase will be limited to only one increment at a time 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):

Safety Biomarker	Baseline value	Any post-dose value observed from baseline to Day 4 (or discharge)
Fibrinogen	within [LLN, ULN]	≤50% of LLN
	< LLN	≤50% of the baseline value
Platelet Count	within [LLN, ULN]	<100,000
	< LLN	≤50% of the baseline value
Prothrombin Time	No restriction	> 4 seconds above the baseline value

LLN: lower limit of normal reference range; ULN: upper limit of normal reference range

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.

2.2.4. **Stopping Rules for mCRM Algorithm**

The mCRM process will be continued until at least one of the following stopping rules is met:

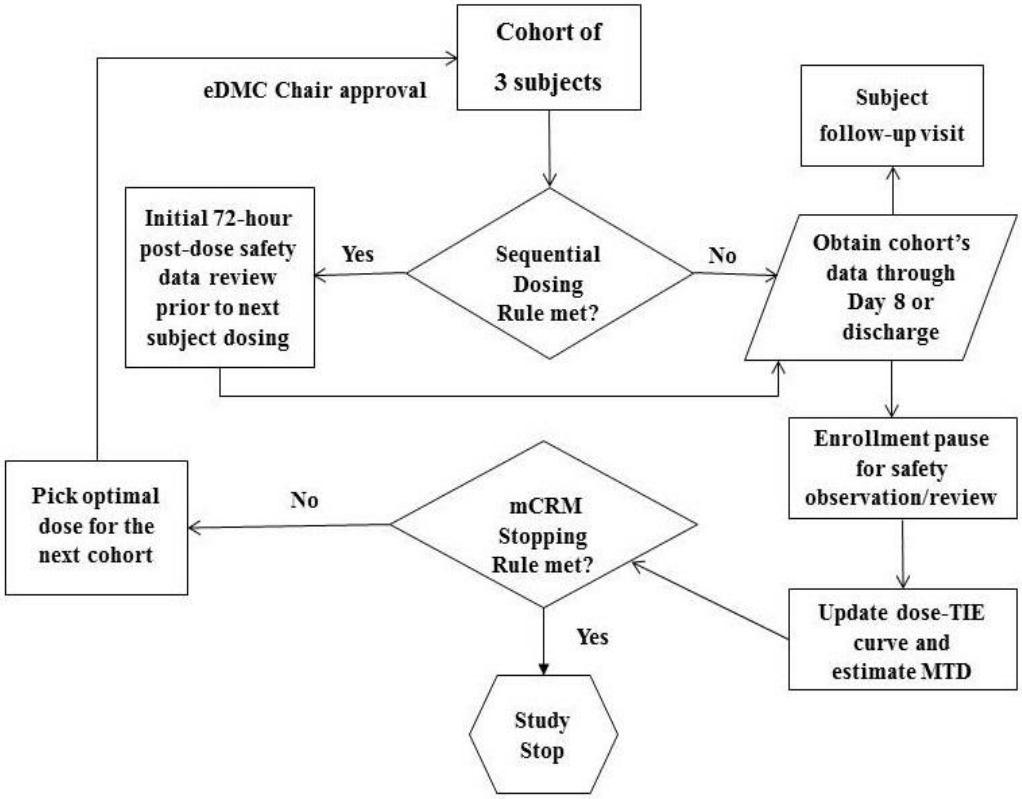
1. *Maximum sample size of 51 subjects has been reached.*

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.*

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

Figure 1. mCRM Design Schematic



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Primary endpoints of the study include the following safety endpoints.

3.1.1. **Treatment emergent TIEs through Day 8**

Thromboembolic and/or ischemic events (TIEs) are defined as any of the listed events at the respective severity grade indicated in Appendix 1. The first primary endpoint is defined as

the frequency of treatment emergent TIEs in subjects treated with PF-05230907 through Day 8. For the respective event to count as a treatment emergent TIE, onset or worsening of the event must occur following treatment with PF-05230907 and during the interval between Day 1 dosing through Day 8.

3.1.2. **Treatment emergent Adverse Events**

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. Any events occurring following the start of treatment or increasing in severity will be counted as treatment emergent. The second and third primary endpoints are defined as follows:

- Treatment emergent AEs as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 8.

- Treatment emergent SAEs as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment through Day 43.

3.1.3. **Treatment emergent laboratory abnormalities**

The fourth primary endpoint is defined as treatment emergent laboratory abnormalities as characterized by type, frequency, and severity through Day 4 (Day 8/discharge for D-dimer).

The clinical laboratory safety parameters in this evaluation include hematology, blood chemistry, Prothrombin Time/International Normalized Ratio (PT/INR), fibrinogen, ATIII, Protein S level, Protein C activity, cardiac troponin I (local or central laboratory), D-dimer (local laboratory), and urinalysis. All test measurements are obtained from the central laboratory unless otherwise noted in the protocol. Any abnormalities occurring after the administration of treatment and increasing in severity from baseline value will be counted as treatment emergent.

3.1.4. **Physical Examination Changes**

The fifth primary endpoint is defined as physical examination changes through Day 8 or discharge, whichever is earlier. Comprehensive physical examination consists 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 comprehensive physical examination is scheduled at screening (baseline) and Day 8 (or discharge).

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. The targeted physical examination is scheduled at Day 2, Day 3, and Day 4.

The results of the comprehensive and targeted physical examinations will be combined to evaluate the changes from baseline through Day 8 (or discharge) for each parameter.

3.1.5. **Vital Signs Changes**

The sixth primary endpoint is defined as vital signs changes through Day 8 (or discharge). Blood pressure, pulse rate, respiratory rate (supine) and temperature will be measured at multiple times specified in Schedule of Activities (SoA) of the Protocol.

3.1.6. **Electrocardiogram (ECG) Results**

The seventh primary endpoint includes the ECG results through Day 8 (or discharge). 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 Day 1, Day 2, Day 4, and Day 8 (or discharge). The Day 1 screening ECG values will serve as each subject's baseline values. 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. Clinically significant abnormalities that represent a change from the Day 1 screening/baseline visit can be recorded as AEs.

3.2. Secondary Endpoint(s)

3.2.1. **Pharmacodynamic Endpoint**

The pharmacodynamic endpoint includes changes in activated partial thromboplastin time (aPTT) and plasma prothrombin fragments 1+2 (PF1+2), after dosing with study drug through Day 2.

3.2.2. **Immunogenicity Endpoint**

The immunogenicity endpoint includes anti-drug antibody (ADA), neutralizing anti-PF-05230907 antibody (NAb), and Factor X activity through Day 43 and/or Day 91 follow-up visit. Blood samples for this endpoint will be collected at the time points described in SoA and analyzed.

3.3. Exploratory Endpoints

3.3.1. **Hemostatic Endpoint**

ICH absolute and CCI *from baseline volume at 24 hours* are exploratory endpoints. A diagnostic brain CT scan completed within 6.0 hours from subject's spontaneous intracerebral hemorrhage symptom onset will provide a baseline ICH volume

assessed by the ABC/2 method for purposes of determining study eligibility. The CT scan completed at baseline and at 24 hours will be sent to the central vendor for final analysis. The ICH volume obtained from the central vendor will be used to assess the ICH absolute and CCI [redacted] from baseline.

Another exploratory endpoint includes *CT parameters that may inform future investigations of PF-05230907 and/or the condition of ICH*.

3.3.2. **Neurological Outcome**

Neurologic function as assessed by the National Institutes of Health Stroke Scale (NIHSS) is an exploratory endpoint. *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.* The NIHSS will be conducted at Screening, Day 1, Day 2, Day 4, Day 43, and Day 91.

3.3.3. **Pharmacokinetics**

PF-05230907 concentration in plasma is an exploratory endpoint. Blood samples will be collected at screening, 5 minutes and 45 minutes post-dose for this evaluation. *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.*

3.3.4. **Exploratory Biomarkers**

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

3.3.4.1. **Pharmacodynamic Biomarkers**

Change in other exploratory biomarkers that may reflect pharmacologic effect of PF-05230907 or ICH progression may be evaluated.

3.3.4.2. **Neuro-inflammation Biomarkers**

Exploratory endpoint includes *potential biomarkers of neuro-inflammation and/or neurological outcomes to better understand ICH and/or its outcomes.*

3.3.5. **Immunogenicity**

Anti-Chinese hamster ovary (CHO) protein antibodies and *anti-paired basic amino acid cleaving enzyme (PACE) furin antibodies* are exploratory endpoints. Blood samples will be collected at screening and Day 43 for this evaluation.

3.3.6. **Health Resource utilization**

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.

3.4. Baseline Variables

3.4.1. **Baseline Definitions**

In this study, "study drug" refers to PF-05230907, "dose group" refers to the group of subjects dosed at the same dose level. Measurements or endpoints will be collected or derived at all visits as specified in the SoA of the protocol. The visits must be performed within the pre-specified visit window as stated in the protocol.

The last available assessment prior to the administration of study drug at Day 1 is defined as "baseline" value or assessment for all analyses unless specifically stated otherwise. If assessment dates are collected, the observed date will be used to determine pre-dose time point from the date of study drug administration for baseline calculation. Otherwise, if an assessment is planned to be performed prior to the administration of study drug in the protocol and the assessment is performed on the same day as the administration of study drug, it will be assumed that it was performed prior to study treatment administration for assessment that the time is not collected or missing.

Analyses involving baseline covariates will only include covariates measured at or before study treatment.

3.4.2. **Baseline Characteristics**

Baseline characteristics include demographics, physical measurements, body mass index, medical history and smoking history. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if the subjects meet the criteria for inclusion in each analysis population prior to releasing the database.

4.1. Full Analysis Set

The Full Analysis Set (FAS) is defined as all enrolled subjects who receive the study drug PF-05230907. Analyses will be performed on the FAS population unless otherwise specified.

4.2. Safety Analysis Set

The safety analysis set is the same as the FAS. All subjects who receive the study drug will be included in the safety analyses and listings. Subjects will be grouped according to the dose level received at study enrollment.

4.2.1. **TIE-evaluable Set**

The TIE-evaluable set includes all subjects who receive PF-05230907. All subjects in the TIE-evaluable set will contribute to the determination of the MTD including subjects who are lost to follow-up prior to completion of the TIE observation period from study enrollment through 7 days post-dose (Day 8). For subject(s) meeting protocol deviations (see Section 4.4) that render the subject non-evaluable for the TIE assessment and necessitating a replacement, the replacement subject will be used instead in sensitivity analyses, and mCRM analyses during the trial when deemed appropriate.

4.3. Other Analysis Sets

For other endpoints including PK, PD, brain imaging, immunogenicity, biomarkers analysis sets are defined as all subjects treated with PF-05230907 who have at least one measurement of the corresponding endpoint or measure of interest.

4.3.1. **Pharmacokinetic Analysis Set**

4.3.1.1. **Concentration Analysis Set**

The PK concentration analysis set is defined as all enrolled subjects treated with PF-05230907 who have at least one measurement of PF-05230907 concentration.

4.3.1.2. **Parameter Analysis Set**

Noncompartmental parameters will not be calculated for the study report due to the short half life (t½) and limited sampling.

4.3.2. **Pharmacodynamic Analysis Set**

The PD analysis set is defined as all enrolled subjects treated with PF-05230907 who have at least one measurement of PD parameters of interest.

4.3.3. **Immunogenicity Analysis Set**

The immunogenicity analysis population is defined as all enrolled subjects treated who have at least one measurement of post-treatment immunogenicity parameters of interest.

4.4. Protocol Deviations

A full list of protocol deviations will be compiled and reviewed by clinician, clinical pharmacologist, and statistician to identify major and minor deviations prior to database release. Different protocol deviations may have impact on different analysis populations. At the discretion of the clinician, clinical pharmacologist, and statistician, major violators might be excluded from impacted analysis populations. The decision and rationale for exclusion will be documented. According to the protocol, any deviations from the PK/PD, 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.*

If dosing error is greater than 20%, then the subject may be excluded from the group statistics of the PK and/or PD analysis when deemed appropriate.

4.4.1. **Deviations Assessed Prior to Enrollment**

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol.

4.4.2. **Deviations Assessed Post-Enrollment**

Deviations that might render a subject non-evaluable for the TIE assessment (excluding subjects who experienced any TIE), potentially necessitating a replacement for the respective cohort during the enrollment period and before the mCRM analysis is run to estimate the MTD include:

- Failure to administer the complete assigned dose of PF-05230907
- Dosing error of sufficient magnitude (underdose or overdose, per the Investigational Product Manual) such that observations from the respective subject would not be reflective of safety for the assigned dose level. Since our dose grid has doses spaced apart by about 25% (Table 2, column 2 from 5 μg/kg onward), actual dose exceeds or falls short of the assigned dose by at least 20% may be considered for a replacement for the respective cohort
- Withdrawal from the study prior to Day 8 (or discharge) for reasons other than study drug-related toxicity
- The informed consent was not signed
- Failure to meet inclusion/exclusion criteria when the resulting eligibility violation(s) adversely impacts the scientific or medical integrity of safety assessments in the respective subject. However, an enrollment or dosing outside of the 6 hours window

is not likely to compromise scientific/medical validity of safety assessments in the respective subject

- Failure to collect the protocol specified safety assessments during the interval from treatment through Day 8 (or discharge)
- Use of prohibited treatments (except when being used to treat an adverse event)

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

This is a study to determine the MTD and assess the safety, tolerability, and PD of PF-05230907 administered once in subjects with ICH. No formal hypothesis testing will be performed. The decision rules for study stopping and MTD determination are described in Section 5.2.

5.2. mCRM design

This study is designed to estimate the MTD, defined as the dose that yields approximately but no greater than the target 15% TIE rate. It employs a modified Continual Reassessment Method (mCRM) design, which utilizes Bayesian methodology to learn the dose-toxicity relationship continuously after each cohort's thromboembolic and/or ischemic event (TIE) data becomes available. Subjects will receive different doses using an adaptive allocation rule with the goal of estimating the MTD. Starting from the second cohort, subjects will be assigned to a dose, from a pre-defined dose grid, that is closest to but not exceeding, the current model-based estimate of MTD based on a one-parameter dose-TIE model, subject to additional dose escalation constraints described in Section 2.2.

5.2.1. **Dose Response Modeling**

The underlying dose-TIE relationship between the probability of TIE events and dose is modeled using a binary endpoint (Y=1: if TIE observed and Y=0: if no TIE observed) and the one-parameter hyperbolic-tangent model.

$$p = \Pr(Y = 1 \mid x; \beta) = f(x; \beta) = \left[\frac{1 + \tanh x}{2}\right]^{\beta} \qquad (1)$$

where x is an adjusted dose which could be computed from an initial 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. In the discrete setting of this trial, where only 15 different doses are available in the dose grid as listed in Table 2 with a starting dose of 5 μg/kg, the dose-TIE model could be replaced by

$$p_i = \Pr(Y = 1 \mid x_i; \beta) = f(x_i; \beta) = \left[\frac{1 + \tanh x_i}{2}\right]^{\beta}, i = 1,\ldots,15$$

where the adjusted doses x_i's are obtained by solving the above equation given β=1 and user supplied vector of p_i's, representing the initial guesses of an anticipated probability of TIE at each dose described in details in the following section.

5.2.2. **Prior distribution**

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 (d) (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

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 TIE data accumulates, it eventually overrules the prior information and later becomes less important.

5.2.3. **Allocation Rule**

The allocation rule is designed to consistently pick the dose with TIE rate closest to but not exceeding the target 15%, therefore maximizing the number of subjects treated at or near that

dose. This is achieved by an adaptive allocation using the model-based estimate of TIE rate at each 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. All subjects in the next cohort will be dosed at the dose level (d_j^*) closest to this estimated MTD but not exceeding it, ie.

$$x_j^* = \max_j [x_j : x_j < f^{-1}(0.15; \hat{\beta})]$$
$$d_j^* \leftrightarrow x_j^*$$

If the current MTD estimate is above the highest dose so far tested, this allocation rule is subject to restriction of maximum 2 dose increments, as specified in Table 2. This restriction is built in the mCRM design module for dose recommendation.

As described in Section 2.2, extensive safeguards and monitoring for subject safety will be implemented. If treatment emergent modulation of one or more of the safety biomarkers fibrinogen, platelet count, and prothrombin time is observed that exceeds pre-specified thresholds during the interval from baseline to Day 4, dose increase will be limited to only one increment at a time. 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.*

5.2.4. **Stopping Rule**

The dose-toxicity model is updated based on the frequency of TIEs in each completed cohort. 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 by the fitted dose-toxicity curve.

3. All doses appear to be overly toxic and the MTD cannot be determined in the current trial setting (stop for futility).

If the stopping rule 1 is met but the stopping rule 2 is not met, not enough subjects have been studied to yield a model-based estimated MTD. If the stopping rule 2 is met, then the MTD will be identified as the current model-based estimated MTD. The earliest time point at which the trial could be stopped early and declare an MTD is after 20 subjects have been

treated and 12 at the MTD dose. For stopping rule 3, the futility stop can be made at any time.

5.2.5. **Simulation 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.

5.3. General Methods

All statistical analyses will be presented in descriptive summaries, graphical displays when appropriate, and data listings by dose group. Data will be reported in accordance with the Pfizer data standards.

Baseline characteristics, disposition, and selected exploratory efficacy data will be summarized based on the FAS by dose group.

TIEs will be summarized based on the TIE-evaluable set. All other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the safety analysis set. PK/PD data will be summarized based on the PK/PD analysis set. Biomarker data will be summarized based on the biomarker analysis set. Immunogenicity data will be summarized based on the immunogenicity analysis set.

5.3.1. **Analyses for Continuous Variables**

Descriptive statistics (number of non-missing values, number of missing values if applicable [ie, n(missing)] , mean, median, standard deviation [SD], minimum, and maximum) for continuous variables will be summarized for all subjects in the corresponding analysis set, by dose group, and by each planned measurement time point if applicable. Inter-quartile ranges (Q1, Q3) and 95% confidence intervals may be provided where meaningful. Geometric mean and coefficient of variation (cv) may be provided as necessary for certain PK parameters.

For all relevant endpoints, the change from baseline at a specific post-treatment visit will be calculated as the difference between the measurement at that visit and the baseline measurement. Fold change, defined as the ratio of the post-treatment to pre-treatment, may be used as needed. For graphical presentation, scatter plots of individual actual values and change from baseline will be generated by scheduled visits, and by dose group when applicable.

5.3.2. **Analyses for Categorical Variables**

Summary statistics including the frequency counts and percentages will be summarized for all subjects in the corresponding analysis set and by dose group for all categorical variables. If there are missing observations, the frequency count and percentage of missingness may be presented as a separate category. For analysis that refers to certain visits, percentages based on the number of subjects who are still present in the study at that visit may also be presented, where appropriate.

5.3.3. **Definition of Time Variables**

5.3.3.1. **Study Day**

Study Day will be derived with sponsor current data standards. Start day of study treatment is the day of the study drug administration, which is Day 1.

The study day for assessments relative to the start of study treatment (eg, adverse event onset) will be calculated as:

Study day = Date of the assessment/event – Date of start of study treatment +1.

The study day will be displayed in all relevant data listings.

5.3.3.2. **Time since ICH Onset to Study Drug Start**

The time in hours from ICH onset to the administration of study drug will be derived from the number of minutes elapsed between the date and time of ICH onset collected from the

"Primary Diagnosis" eCRF page and the start date and time of study drug administration collected from the "Dosing Record" eCRF page.

5.3.3.3. **Duration of Study Treatment**

The duration of the study drug administration will be derived from the number of minutes elapsed between the start date and time of dose administration, and the stop date and time of dose administration collected from the "Dosing Record" eCRF page.

5.3.3.4. **Duration of Hospital or Outpatient Rehabilitation Stay**

Health resource utilization is an exploratory endpoint. The hospital admission and discharge dates are collected for four categories of hospital unit: Intensive Care Unit (ICU), general ward (medical/surgical unit), in-patient rehabilitation center, and Other hospital units. The outpatient rehabilitation center admission and discharge dates are also collected. The duration of stay for each type of hospital unit or outpatient rehabilitation center will be derived as follows:

For non-missing discharge date:

duration of stay (days) = date of discharge – date of admission

For an ongoing stay, the date of last contact can be derived from the assessment dates described in Section 5.4.4.2:

duration of stay (days) = date of last contact – date of admission

The duration of main hospital stay (ICU/general ward) includes the duration of stay in ICU and general ward. It can be derived as follows:

ICU/general ward admission date = min (non-missing date of ICU admission, non-missing date of general ward admission)

ICU/general ward discharge date = max(non-missing date of ICU discharge, non-missing date of general ward discharge)

Maximum length of ICU/general ward stay = ICU/general ward discharge date – ICU /general ward admission date

duration of main hospital stay = Maximum length of ICU/general ward stay – duration of stay in hospital units other than ICU and general ward during the ICU/general ward maximum stay period

If a discharge date is missing and the stay is ongoing, the date of last contact will be used to calculate the corresponding duration. In the event of death during hospital or outpatient rehabilitation stay, the date of death will be used to calculate the duration of the corresponding health facility unit.

For each type of hospital unit or outpatient rehabilitation center, if a subject is admitted and discharged on the same date, the corresponding duration will be assigned as 0.5 day.

5.3.4. **Standard Derivations and Reporting Conventions**

The following conversion factors will be used to convert days into weeks and months: 1 week = 7 days, 1 month = 30.4375 days

Demographics and physical measurements:

- Age (years):
  - (date of study treatment start - date of birth + 1) / 365.25;
  - In case of missing day, the missing day will be imputed as 15 for the calculation
  - In case only year of birth is given:
    Age (years) = (year of study treatment start – year of birth).

The integer part of the calculated age will be used for reporting purposes.

The following conversion factors will be used to convert pounds into kilogram (kg), inches and centimeters (cm) into meter (m): 1 pound = 0.4536 kg, 1 inch = 0.0254 m, 1 cm = 0.01 m.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. Rounding can be performed to the closest integer or the targeted decimal place using the common mid-point between the two consecutive values. Eg, 6.1 to 6.4 can be rounded to an integer of 6, and 6.501 to 6.549 can be rounded to 6.5.

5.3.5. **Unscheduled Visits**

Generally, data collected at unscheduled visits will be included and analyzed for all analyses in the same fashion as the data collected at scheduled visits except where otherwise noted. Unless otherwise noted, descriptive statistics by nominal visit such as laboratory measurements and vital signs will include only data from scheduled visits unless the scheduled visit measurement is missing, and needs to be replaced by an unscheduled visit that fall into the time window permitted for analysis purpose (see Section 5.4.5).

5.4. Methods to Manage Missing Data

5.4.1. **Missing Data**

All data will be evaluated as observed, and no imputation method for missing values will be used unless otherwise specified.

In all data listings, imputed values (if any) will be flagged. For missing statistics, for example, the measure of variability (SD) cannot be computed when N=1, 'ND' (Not Done) or 'NA' (Not Applicable) will be presented.

5.4.2. **Pharmacokinetic Concentrations and Parameters**

5.4.2.1. **PF-05230907 Concentrations Below the Limit of Quantification**

In all data presentations except listings, PF-05230907 concentrations assayed as below the limit of quantification (BLQ) will be set to zero. In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.

5.4.2.2. **Deviations, Missing Concentrations and Anomalous Values**

In summary tables and plots of median profiles, concentrations will be set to missing if at least one of the following cases is true:

1. A concentration has been collected as ND (Not Done) or NS (no sample).
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.4.2.3. **Pharmacokinetic Parameters**

Noncompartmental parameters will not be calculated for the study report.

5.4.3. **Laboratory Assays Below the Limit of Detection**

Assays for some laboratory parameters have lower limits of detection (LLD). If the assay values are below the LLD, then it is equally likely to be anywhere between 0 and the LLD. In this case, the best single prediction of the value ignoring all other data from the subject is in the middle of 0 and the LLD value. As a general guidance for all data presentation except listings, the half of LLD value will be imputed for a laboratory assay value reported as below the LLD. For example,

1. For TFPI, value of "<3.0 ng/mL" will be imputed as 1.5 ng/mL.
2. For Cardiac Troponin I, value "<0.02 ug/L" will be imputed as 0.01 ug/L.
3. For D-dimer, value of "<190 ng/mL" will be imputed as 95 ng/mL.

In data listings assays with values below LLD will be reported as '<LLD', where LLD will be replaced with the LLD value for the corresponding laboratory parameter.

5.4.4. **Handling of Incomplete Dates**

5.4.4.1. **Safety Endpoints**

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied (eg, partial onset and resolved dates for AEs and concomitant medications will be imputed according to Pfizer standard algorithms). Dates that are derived for missing data by the Pfizer standard algorithms are bounded by square brackets accompanied by the footnote, "Days in brackets are imputed days derived from missing or incomplete dates." in relevant data listings.

5.4.4.2. **Imputation Rules for Date of Last Contact**

The date of last contact will be derived for subjects not known to have died at the analysis cut-off using the latest complete date among the following:

- All subject assessment dates (blood draws including clinical laboratory, vital signs, immunogenicity sample, mRS, NIHSS, and health resource utilization).
- AE start and resolved dates

Only dates associated with actual examinations of the subject will be used in the derivation. Dates associated with a technical operation unrelated to subject status such as the date a blood sample was processed will not be used. Assessment dates after an analysis database cut-off date will not be applied to derive the last contact date.

5.4.5. **Extended Time Post Dose Visit Window**

The Schedule of Activities table in the study protocol defined the visit window and the study activities should take place within these visit windows. However, some activities such as laboratory testing, might occur out of the protocol specified visit window in reality. For the purpose of statistical analysis, Table 4 defines extended visit windows. If the deviation is determined not to compromise scientific integrity of the assessment upon review, and the result is obtained within the New Study Specified Visit Window for Statistical Analysis, then the result will be included in the analysis to minimize missing data issue.

Table 4. Extended Visit Window for Analysis

Visit Window Specified in Schedule of Activities Table in the Study Protocol		New Study Specified Visit Window for Statistical Analysis		
Study Day	Time Post Dose Visit Window	Extended Visit Window	Window Start	Window End
Day 1 Screening	Up to 6.0 hours pre-dose	[-24, 0] hr	-24 hr	0 hr

Table 4. Extended Visit Window for Analysis

Day 1	Hr 0	[-4,0] hr	-4 hr	0 hr
Day 1	Hr 0 Min 5 (±2 min)	±4 min	1 min	9 min
Day 1	Hr 0 Min 45 (±15 min)	±30 min	15 min	75 min
Day 1	Hr 3 and Hr 9 (±30 min)	±1 hr	2 hr, 8 hr	4 hr, 10 hr
Day 2	24 Hr (±6 hr)	±8 hr	16 hr	32 hr
Day 3	48 Hr (±6 hr)	±10 hr	38 hr	58 hr
Day 4	72 Hr (±6 hr)	±12 hr	60 hr	84 hr
Day 8/discharge	±24 hr	±48 hr	120 hr *	216 hr *
Day 43	±7 Days	±12 Days	720 hr (Day 31)	1296 hr (Day 55)
Day 91	±7 Days	±12 Days	1872 hr (Day 79)	2448 hr (Day 103)

* For discharge day other than Day 8, use ±48 hr from the discharge day to construct the extended visit window

If there are multiple measurements within a visit window, the measurement taken at the time that is closest to the scheduled visit time point will be used for summary statistics at that time point unless otherwise stated.

6. ANALYSES AND SUMMARIES

Refer to Section 3 for definitions of endpoints, Section 4 for definitions of analysis sets, and Section 5.3 for general methodology.

6.1. Primary Endpoints

6.1.1. **Treatment emergent TIEs through Day 8**

The primary analyses will be based on the TIE-evaluable set. Treatment emergent TIEs will be listed and summarized overall and by dose group. The summary Tables include:

- Treatment emergent TIEs (all causalities) by system organ class and preferred term
- Treatment emergent TIEs (treatment related) by system organ class and preferred term
- Incidence and severity of treatment emergent TIEs (all causalities, treatment related)

As discussed in Section 5.2, the TIE data from the current cohort (and previous cohort[s]) will be utilized for the mCRM dose-toxicity modeling along with clinical and eDMC oversight to determine the MTD. The following Figures will be generated:

- Vertical bar chart of the number of treatment emergent TIEs by dose group used in the mCRM dose-toxicity modeling
  - Estimated Dose-TIE toxicity response curve with 95% confidence interval around the fitted curve, superimposed on the number of subjects allocated to each dose group in a vertical bar chart format, and the observed proportion of treatment emergent TIE at each dose level
- Allocation of subjects at each dose and corresponding TIE toxicity response (red dot denotes treatment emergent TIE) showing how dose-escalation scheme progresses over time via the order of study enrollment and observed number of treatment emergent TIEs

For the interim analysis of the treatment emergent TIEs, refer to Section 7 for details.

6.1.1.1. **Sensitivity/Robustness Analyses**

One primary objective of this study is to determine the MTD of the study drug. The mCRM dose-toxicity modeling is based on an "intent-to-treat" approach that the subject's assigned dose group is used in the modeling, estimation of MTD, and dose-recommendation for the next cohort based on available data during the safety review period after each respective cohort completes dosing. Sensitivity analysis will be conducted to assess the robustness of the MTD determination based on weight-based dosing. A confidence interval around the MTD may be calculated where appropriate. The relationship of the actual dose administered in µg with treatment emergent TIE occurrence will also be evaluated.

6.1.2. **Other Primary Safety Endpoints**

Other primary safety endpoints will be summarized descriptively by dose group. The endpoints include treatment emergent AEs through Day 8 and SAEs through Day 43 as characterized by type, frequency, severity, timing, seriousness and relationship to study treatment; treatment emergent laboratory abnormalities through Day 4 (Day 8/discharge for D-dimer); physician examination changes, vital signs changes, and ECG results through Day 8 (or discharge). Listings of data will be generated by dose group. Refer to Section 6.6 for details.

6.2. Secondary Endpoint(s)

6.2.1. **Pharmacodynamic Endpoint**

The pharmacodynamic endpoint includes aPTT or PTT and PF1+2, within 2 days of dosing. Maximum change from baseline and area under the effect curve (AUEC) of change from baseline will be calculated for aPTT or PTT, and PF1+2.

The PD endpoints will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. The summaries will be provided in actual values and change from baseline. Descriptive statistics including N, arithmetic mean, median, SD, minimum, and maximum will be used to summarize maximum change from baseline and AUEC of change from baseline.

6.2.2. **Immunogenicity Endpoint**

Immunogenicity analysis will be conducted on the immunogenicity analysis set as defined in Section 4.3.3.

ADA, Nab and factor X activity assay results will be summarized by dose group and visit. The number and percentage of subjects with positive or negative ADA immune response and NAb immune response will be summarized by dose group in tabular format.

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.

6.3. Exploratory Endpoint(s)

Exploratory efficacy measures include hemostatic endpoints (ICH absolute and CCI from baseline volume) and neurological outcomes (mRS and NIHSS).

Descriptive statistics will be used to summarize selected exploratory endpoints by dose group, where appropriate. Change from baseline for selected continuous measure will be summarized descriptively. Listings of all exploratory endpoint information will be generated by dose group.

Analyses to be conducted on each exploratory endpoint and associated measures at other time points are described in each subsection below.

6.3.1. **Hemostatic Endpoint**

6.3.1.1. **ICH change from baseline**

ICH absolute and CCI *from baseline volume at 24 hours* are exploratory endpoints. ICH volume obtained from central vendor will be used for the evaluation of these endpoints to reduce variability and enhance accuracy of the results reported.

Absolute change from baseline and CCI from baseline in ICH volume will be summarized descriptively.

6.3.1.2. **CT parameters**

Another exploratory endpoint includes CT parameters that may inform future investigations of PF-05230907 and/or the condition of ICH.

Actual values in edema volume contiguous with the area of hemorrhage, and volume of blood in ventricle will be summarized descriptively and presented in tabular format, where appropriate. New onset ischemic components not contiguous with the area of hemorrhage, absent at baseline but present at 72 hours will also be summarized if applicable. The number and percentage of subjects in each of the following categories may be summarized in tabular format:

- location of origin of bleed
- location of ischemic component
- presence of "swirl sign" on baseline CT
- presence of spot sign on baseline CT angiogram (if applicable)
- pre-existing ischemia not contiguous with hemorrhage
- location of pre-existing ischemia not contiguous with hemorrhage

- new onset ischemia not contiguous with hemorrhage
- location of new onset ischemia not contiguous with hemorrhage

The diagnostic brain CT scan completed within 6.0 hours from subject's spontaneous ICH symptom onset will provide a baseline assessment of ICH volume assessed by the ABC/2 method, ICH_{ABC}, for purposes of determining study eligibility. Correlation between the baseline ICH volume obtained by ABC/2 method and the central vendor will be assessed. In addition, the time since ICH onset to study drug start, the time elapsed between baseline CT scan and the study drug start time will be summarized.

6.3.2. **Neurological Outcome**

Neurologic function as assessed by the NIHSS is an exploratory endpoint. Actual values at scheduled visits will be summarized descriptively.

6.3.3. **Pharmacokinetics**

PF-05230907 concentration in plasma is an exploratory endpoint. There will be C_{5min} and C_{45min} denoting the plasma concentration at 5 minutes and 45 minutes post-dose, respectively. *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 (t½) and limited sampling, noncompartmental parameters will not be calculated for the study report.*

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations will be presented in tabular form by dose group and nominal time.
- Dose-normalized C_{5min} and C_{45min} will be summarized using data pooled across dose groups in which different PF-05230907 doses were administered.

As data permit, pharmacokinetic data from this study may be analyzed using modeling approaches and may also be pooled with data from other studies to investigate any association between PF-05230907 exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.3.4. **Exploratory Biomarkers**

6.3.4.1. **Pharmacodynamic Biomarkers**

Change in other exploratory biomarkers that may reflect pharmacologic effect of PF-05230907 or ICH progression may be evaluated.

For aPTT or PTT, results obtained through Day 4 will be included in the analyses described in Section 6.2.1 to evaluate the changes from baseline. For other exploratory biomarkers available, they will be analyzed in the same manner as described in Section 6.2.1.

6.3.4.2. **Neuro-inflammation Biomarkers**

Exploratory endpoint includes *potential biomarkers of neuro-inflammation and/or neurological outcomes to better understand ICH and/or its outcomes.*

Listing of available neuro-inflammation biomarker data will be generated.

6.3.5. **Immunogenicity**

Immunogenicity analysis will be conducted on the immunogenicity analysis set as defined in Section 4.3.3. Listing of baseline values and changes from baseline to Day 43 in Anti-CHO protein antibodies and anti- PACE furin antibodies will be generated. A summary of positive anti-CHO or anti-PACE furin antibody immune responses may be generated when applicable.

6.3.6. **Health Resource utilization**

Duration of stay in ICU unit, general ward (medical/surgical unit), main hospital stay including ICU/general ward, inpatient rehabilitation center, and other hospital units will be displayed in listings. The duration of stay for each type of hospital unit or outpatient rehabilitation center will be derived according to Section 5.3.3.4.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. **Baseline Summaries**

The following analyses will be based on the FAS overall and separately by dose group.

6.5.1.1. **Demographic Characteristics**

Demographic characteristics and physical measurements will be summarized descriptively.

- Age (years): summary statistics; Age categories : <65 years, ≥65 years
- Sex: Male, Female
- Race: White, Black, Asian, Other
- Ethnic origin: Hispanic/Latino (Yes/No)
- Physical measurements include weight (kg), height (cm), and Body Mass Index (BMI) (kg/m^2)

Site codes will be used for the determination of the subject's geographic region.

The listing of demographics and baseline characteristics by dose group will include the following information: subject ID, dose group, age, sex, race, ethnicity, height (cm), weight (kg), and BMI (kg/m^2).

6.5.1.2. **Medical History and Smoking History**

Medical history will be summarized descriptively from the 'Significant Medical History' eCRF page. In addition, medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and MedDRA preferred term as event category and MedDRA primary system organ class (SOC) as summary category. Each subject will be counted only once within each SOC or preferred term. It will be displayed in terms of frequency tables ordered by primary SOC and preferred term in alphabetical order.

Smoking history will be summarized by the classification: Smoker, Ex-Smoker, and Never Smoked.

Listings of the medical history and smoking history by dose group will be generated.

6.5.1.3. **Intracerebral Hemorrhage Characteristics**

Intracerebral Hemorrhage (ICH) baseline information including date of ICH onset, time of ICH onset, time since ICH onset to study drug start, date of ICH evaluation including risk factors, ICH volume at baseline CT scan (mL) by ABC/2 assessment and by central vendor analysis, and vascular malformation ruled out (Yes/No) will be summarized descriptively. Listing of the relevant information collected from the "Primary Diagnosis", "Dosing Record", and "Intracerebral Hemorrhage Details" eCRF pages will be generated by dose group. Refer to Section 5.3.3.2 for the derivation of the time since ICH onset to study drug

start. Analysis results obtained from central vendor will also be summarized and included in the description of baseline ICH characteristics.

6.5.2. **Study Conduct and Subject Disposition**

The following analyses will be performed based on the FAS overall and separately by dose group.

6.5.2.1. **Subject Disposition**

Summary of subject disposition by dose group will be provided. The percentages will be calculated based on the number of subjects in the FAS where appropriate.

- Total number of subjects screened overall
- Number of subjects assigned to study treatment
- Number of subjects who completed the study
- Number and percentage of subjects who withdrawn from the study overall and by primary reason for withdrawal
- Number and percentage of subjects who entered outpatient follow-up

In addition, the number and percentage of treated subjects by center will be summarized.

6.5.2.2. **Protocol Deviations**

All protocol violations that impact the subject safety, the conduct of the study, and/or the study evaluation will be reported. These include

- Subjects who are dosed on the study even though they did not strictly meet the inclusion/exclusion criteria
- Subjects who receive an incorrect dose
- Deviations from Good Clinical Practice (GCP), and/or the conduct of the study

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria and other criteria presented in the protocol. Refer to Section 4.4 for details.

6.5.3. **Study Treatment Exposure**

Analyses of exposure to study drug will be based on the safety analysis set by dose group assigned at enrollment. The duration of study drug administration will be summarized and included in the listing of study drug administration based on the information collected from the "Dosing Record" eCRF form.

The summary of study treatment exposure and compliance will include the following information:

- Treatment duration (minutes)
- Concentration (ng/mL)
- Actual dose administered (µg)
- Actual dose administered/ Baseline weight (µg/kg)

Sensitivity analyses will be conducted to assess the robustness of study conclusion based on the actual dose administered. For weight-based dosing evaluation, the weight-adjusted dose is calculated as the actual dose administered/baseline weight (µg/kg). The last available weight of the subject measured on or prior to the day of dosing will be used. If actual weight cannot be obtained prior to dosing, the earliest post-dose directly measured weight will be used for the evaluation. For flat dose evaluation, the treatment dose level is the actual dose administered in µg.

Refer to Section 6.3.3 for PK analysis of the drug concentration.

6.5.4. **Concomitant Medications and Non-Drug Treatments**

The analyses will be based on the safety analysis set overall and by dose group.

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. All concomitant treatments and medications taken during the study will be reported with the indication and start and stop dates of administration.

Listings of prior treatments and medications, concomitant medications and treatments will be created from the information collected on the 'Previous and Concomitant Drug Treatment' eCRF page. The concomitant drug start and stop day relative to the date of PF-05230907 administration will be shown.

Summary of prior and concomitant medications will include the number and percentage of subjects by Anatomical Therapeutic Chemical (ATC) Classification levels and preferred term. A subject will be counted only once within a given drug class and within a given drug name, even if he or she received the same medication at different times. If any prior or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level coded term, it will be summarized under 'Unavailable ATC classification' category.

All prior and current non-drug treatment and/or procedures will be summarized according to the 'Previous and Current Non-Drug Treatment/Procedure' eCRF page. Number and

percentage of subjects with concurrent non-drug treatment/procedure will be tabulated overall, by dose group, and by reason for non-drug treatment/procedure. Listing of previous and current non-drug treatment/procedure will be generated with start day and stop day relative to the date of PF-05230907 administration.

6.6. Safety Summaries and Analyses

Safety analyses will be conducted based on the safety analysis set. All safety endpoints as described in Section 3 will be summarized descriptively in tabular and/or graphical format and listed, where appropriate, in accordance with Pfizer data standards. Details of the analyses are described in the following sections.

6.6.1. **Adverse Events**

Treatment emergent TIEs through Day 8, treatment emergent adverse events (TEAEs) through Day 8, and treatment emergent SAEs through Day 43 are primary endpoints. Any adverse events occurring following the start of treatment or increasing in severity during the observation period will be counted as treatment emergent. In addition, three categories of interest through Day 91 are defined as follows:

- **Related Adverse Events:** adverse events with relationship or unknown relationship to study treatment reported by the investigator and recorded on the AE eCRF page with CAUSALITY = YES/UNKNOWN or missing

- **Adverse Events Leading to Permanent Treatment Discontinuation or withdrawal from study:** adverse events leading to permanent discontinuation of study treatment or withdrawal from study as recorded on the AE eCRF page, Action taken with study treatment dose = Permanently discontinued or subject withdrawn from study

- **Adverse Events with severity Grade 3 or higher:** adverse events of Grade 3 to Grade 5 as recorded on the AE eCRF page

The corresponding AE listings will include all AEs (whether treatment emergent or not), study day, and the relevant information collected from the AE eCRF pages for the primary endpoints, and the categories of interest aforementioned. The incidence of AEs that fall within the respectively reporting period will be summarized and listed by body system, severity and causality by dose group. AEs outside the period considered will be flagged in the listings.

Adverse events will be summarized by worst severity per subject, using the latest version of MedDRA preferred term as event category and MedDRA primary system organ class (SOC) body term as Body System category. The number and percentage of subjects with the AE in each categories of interest will be summarized overall and by dose group, by

primary SOC and preferred term in decreasing frequency observed in all dose groups combined.

Each subject will be counted only once within each SOC or preferred term. If a subject experiences more than one AE within a SOC or preferred term for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

In case a subject has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

6.6.2. **Laboratory Data**

The assessment on the laboratory parameters will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter. Laboratory results for some parameters may be classified according to the CTCAE criteria version 4.03. Laboratory results that are not part of CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit. In addition, the summary tables and data listings for the subjects who meet the criteria for potentially clinically significant abnormalities in Appendix 2, will be presented. All investigators' comments on the safety data will be listed and reviewed.

Incidence and magnitude of treatment emergent abnormal findings in the laboratory safety parameters will be summarized descriptively by dose group.

As described in Section 2.2.3, dose increase will be limited to only one increment at a time if treatment emergent modulation of fibrinogen, platelet count, or prothrombin time in excess of pre-specified thresholds is observed during the interval from baseline to Day 4 (or discharge). Listing of subjects who meet the safety biomarker criteria for dose escalation adjustment will be generated by dose group.

For Tissue Factor Pathway Inhibitor (TFPI), baseline values will be summarized descriptively. For available Prothrombin G20210A Mutation and Factor V Leiden Mutation, the number and percentage of subjects with the mutation will be summarized overall and by dose group.

For Prothrombin Time/International Normalized Ration (PT/INR), Anti-thrombin III (ATIII), D-dimer, Protein S level, Protein C activity, and cardiac Troponin I, actual values will be summarized descriptively. For safety analyses the central laboratory results for cardiac troponin I will take precedence over local determinations for cardiac troponin T.

6.6.3. **Physical Examination**

The results of the comprehensive and targeted physical examinations will be combined to evaluate the changes from baseline through Day 8 (or discharge) for each site parameter according to the categories: Positive Change (Abnormal to Normal); No Change (Normal to

Normal or Abnormal to Abnormal); Negative Change (Normal to Abnormal) . Number and percentage of subjects with abnormal findings will be summarized by body system over time. For subjects with any abnormal findings, their physical examination assessments will be listed by dose group.

6.6.4. **Vital Signs**

Vital signs changes through Day 8 (or discharge) is a primary endpoint. All vital sign parameters will be summarized using descriptive statistics of actual values and changes from baseline for each visit over time. Vital signs at discharge date will be summarized separately.

6.6.5. **Electrocardiogram**

ECG parameters include QT interval, QTc interval, RR interval, heart rate, PR interval, QRS complex, and the QT interval corrected for heart rate by the Fridericia's formula, denoted as QTcF, or QTc (Fridericia's Correction) collected from the "ECG" eCRF page. For each ECG parameter, actual values and changes from baseline will be summarized descriptively. For comparison to baseline ECG, the number and percentage of subjects in each of the categories: Less abnormal, No significant change, More abnormal, and No baseline will be summarized by dose group over time. In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

If more than one ECG is collected at a nominal time post dose (for example, triplicate ECGs to confirm a clinically significant abnormality), the mean of the continuous measurements will be used to represent a single observation at that time point. For categorical variable, a working score of 1, 0, -1 will be assigned to the comparison to baseline ECG category "Less abnormal", "No significant change", and "More abnormal", respectively. The category closest to the mean working score derived from multiple ECGs within a scheduled visit time window will be used in the frequency count.

For subjects with ECG abnormalities, and ECG parameters meeting the criteria of potential clinically significant abnormal results (see Appendix 2), their results will be displayed in separate listings by dose group.

6.6.6. **Other Safety Data**

6.6.6.1. **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 as shown in Appendix 3.

Results for thrombosis clinical probability scores, DVT and PE total scores will be summarized descriptively based on the greatest reported score per subject by dose level. Probability for DVT will be summarized according to the following categories:

Low probability: DVT total score < 1

Moderate probability: DVT total score is 1 or 2

High probability: DVT total score > 2

Likely: DVT ≥ 2

Probability for PE will be summarized according to the following categories:

Low probability: PE total score < 2

Moderate probability: PE total score is 2-6

High probability: PE total score > 6

Likely: PE > 4

Listing of subjects who are "likely" to have DVT or PE will be generated.

6.6.6.2. **Brain Imaging Study and Doppler Ultrasound**

A CT or MR scan will be completed as indicated in the SoA of the protocol and reviewed locally by a qualified physician for evidence of a treatment emergent ischemic event. Doppler ultrasonography of the lower extremities will be conducted at screening and at 72 hours post-dose (and discharge/Day 8 if applicable). Listing of Brain imaging study [CT ± MRI] scan results, and Doppler ultrasound of the lower extremity will be generated by dose group. New onset (ie, absent at baseline, present at 72 hours) ischemic findings not contiguous with the area of hemorrhage will be summarized. Treatment emergent abnormal Doppler ultrasound results will be listed and summarized.

6.7. Other Assessments

6.7.1. **Glasgow Coma Scale**

Screening Glasgow Coma Scale (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 assessment closest to the study drug start time prior to dosing will be used for baseline assessment. Listing of GCS assessments will be generated.

6.7.2. **Modified Rankin Scale**

The modified Rankin Scale is ordered categorical data ranging from zero indicating no symptoms to six for a dead outcome (see Appendix 4). Listing of the actual values and change from baseline at scheduled visits will be generated.

7. INTERIM ANALYSES

7.1. Introduction

This is a Phase 1b, open-label study to evaluate the safety, tolerability, and determine the MTD of PF-05230907 in subjects with ICH. There is no formal statistical interim analysis planned for the study but an external Data Monitoring Committee (eDMC) is set up for interim data monitoring. In addition, sequential dosing can occur within a cohort of 3 subjects, and will occur after each cohort completes dosing to allow the Sponsor to review the safety data as additional safeguards for subject safety. Refer to Section 2.2.2 for details.

7.2. Determination of the MTD

After each cohort completes dosing and TIE data through Day 8 becomes available for the respective cohort, all available TIE data will be analyzed to update the dose-toxicity model as described in Section 5.2. The MTD will be estimated and the dose will be recommended for the next cohort of subjects based on the mCRM dose-toxicity modeling.

Other safety biomarker data (Section 2.2.3) from the trial will also be taken into consideration to provide clinical oversight in determining the dose for the next cohort.

7.3. External Data Monitoring Committee (eDMC)

The 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, the following criteria are implemented to trigger an automatic eDMC review of safety at a respective dose level.

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.

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.

7.4. Interim Analyses and Summaries

This section describes the analyses and summaries that will be conducted solely for the interim.

7.4.1. **Safety Review during Sequential Dosing Pause within a Cohort**

When a cohort meets the criteria for sequential dosing (see Section 2.2.2.1), safety review will take place during the enrollment pause. Clinical observation results collected on the respective subject during the initial 72-hour period following dosing will be reviewed by the medical monitor. The information includes treatment emergent adverse events (TEAEs), SAEs, vital sign changes, ECG changes, brain imaging study (CT±MRI) scan, Doppler ultrasound of the lower extremity and cardiac troponin I (and cardiac troponin T where applicable). Other available laboratory test results at the time of this safety review will also be assessed.

The enrollment will resume when the medical monitor completes the safety review.

7.4.2. **Safety Review between Cohorts**

Safety data through Day 7 post-dose (Day 8) comprised of the following information will be reviewed by the medical monitor and eDMC Chair. The information include summary of significant findings in treatment emergent adverse events (TEAEs), SAEs, vital sign changes, ECG changes, brain imaging study (CT±MRI) scan, Doppler ultrasound of the lower extremity, fibrinogen, platelet count, PT, and cardiac troponin I (and cardiac troponin T where applicable) of the respective cohort and all data available by dose group. Other available laboratory test results at the time of this safety review will also be assessed.

Summary and listings of available PK and PD data will be provided to help assess where clinical exposure is relative to the No Observed Adverse Effect Level (NOAEL) and assess benefit risk. However, this is not a safety data review requirement to proceed to the next cohort. Refer to Section 2.2.2.3 for details of the eDMC review of cohort safety data, and Section 2.2.2.2 for all requirements needed to proceed to the subsequent cohort.

7.4.2.1. **eDMC Meetings for Cumulative Safety Review**

The eDMC will meet regularly per the eDMC charter to review cumulative safety data. In addition to the safety, available PK and PD information including the pharmacodynamic endpoint data regarding the changes in activated partial thromboplastin time (aPTT) and plasma prothrombin fragments 1+2 (PF1+2), after dosing with study drug through Day 2 will be provided for the eDMC meeting review. Analyses of all available safety data, PK and PD data through the database cut-off date will be conducted for the interim safety review. Relevant Listings, Figures, and Tables summarizing the primary endpoints information will be provided. Refer to Section 6 for details.

8. REFERENCES

Garrett-Mayer E. The continual reassessment method for dose-finding studies: a tutorial. Clinical Trials. 2006; 3(1): 57-71.

Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the continual reassessment method for phase I studies. Stat in Medicine 1995; 14: 149-61.

Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke 1996;27:1304-5.

9. APPENDICES

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

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
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
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

Adverse Event (Grade Defining a TIE)	**Grade and Description**
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
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
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
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. Criteria for safety values of potential clinically significant abnormal results

Category/Test	Abnormal values of potential clinical significance for review
Hematology	
Hemoglobin	<0.8 times LLN
Hematocrit	<0.8 times LLN
RBC Count	<0.8 times LLN
MCV	<0.9 times LLN or >1.1 times ULN
MCH	<0.9 times LLN or >1.1 times ULN
MCHC	<0.9 times LLN or >1.1 times ULN
Platelets	<0.5 times LLN or >1.75 times ULN
Leukocytes	<0.6 times LLN or >1.5 times ULN
Total Neutrophils (Abs)	<0.8 times LLN or >1.2 times ULN
Eosinophils (Abs)	>1.2 times ULN
Basophils (Abs)	>1.2 times ULN
Lymphocytes (Abs)	<0.8 times LLN or >1.2 times ULN
Monocytes (Abs)	>1.2 times ULN
Chemistry	
Total bilirubin	>1.5 times ULN
Direct bilirubin	>1.5 times ULN
Indirect bilirubin	>1.5 times ULN
AST	>3 times ULN
ALT	>3 times ULN
Alk Phosphatase	>3 times ULN
Creatinine	>1.3 times ULN
BUN	>1.3 times ULN
Uric acid	>1.2 times ULN
Sodium	<0.95 times LLN or >1.05 times ULN
Potassium	<0.9 times LLN or >1.1 times ULN
Chloride	<0.9 times LLN or >1.1 times ULN
Bicarbonate	<0.9 times LLN or >1.1 times ULN
Calcium	<0.9 times LLN or >1.1 times ULN
Albumin	<0.8 times LLN or >1.2 times ULN
Total protein	<0.8 times LLN or >1.2 times ULN
Creatine Kinase	>2.0 times ULN

Category/Test	Abnormal values of potential clinical significance for review
Miscellaneous Laboratory Data	
D-dimer	>ULN
Prothrombin G20210A Mutation	Present
Factor V Leiden Mutation	Present
PT	Prolongation by >4 seconds above baseline
INR	≥1.5
Fibrinogen	≤0.5 times LLN when baseline is within normal range
	≤0.5 times baseline when baseline <LLN
Anti-Thrombin III (ATIII)	<LLN and ≥ 20% decrease from baseline
Protein C activity	<LLN
Protein S level	<LLN
Cardiac Troponin I	>ULN
Urinalysis	
Urine WBC	≥20/HPF
Urine RBC	≥20/HPF
Urobilinogen	≥1
Urine Bilirubin	≥1
Vital Signs	
Pulse Rate	Supine: <40 or >120 bpm
Blood Pressure	Systolic <90 mm Hg or ≥30 mm Hg change from baseline
	Diastolic <50 mm Hg or ≥20 mm Hg change from baseline
Electrocardiogram	
PR interval	≥300 msec; ≥25% increase when baseline >200 msec
	Increase ≥50% when baseline ≤200 msec
QRS interval	≥140 msec; ≥50% increase from baseline
QTc interval	≥500 msec

Note:

LLN: lower limit of normal reference range

ULN: upper limit of normal reference range

Appendix 3. Thrombosis Clinical Probability Scores

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 4. Modified Rankin Scale (mRS)

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