Protocol B7841010

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

Statistical Analysis Plan
(SAP)

Version: 2.0

Date: 20 May 2021

[redacted]

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 19 Dec 2019	Original 24 Oct 2019	N/A	N/A
2 20 May 2021	Amendment 1 22-Oct-2020	Update according to Protocol Amendment 1; Clarification of prior version.	• Primary Endpoint: Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs) and withdrawals due to TEAE; Day 1 up to Day ~~28~~ 42. (Section 2.1, Section 3.1) • Changed "~~one way~~" to "single-arm". (Header, Section2.2) • Added clarification that tissue factor pathway inhibitor (TFPI) samples were for both total and free TFPI. (Section 2.1, Section 3.2.2, Section 3.4, Section 6.2.2) • Added: The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator. If Day 42 visit and the Screening visit of B7841005 occur on the same day, it must be a clinic visit. (Section 2.2) • The maximum total duration of the study for a single participant, from initial screening to final follow up, will be approximately ~~2~~ 2.5 months. (Section 2.2) • Added clarification: Participants who complete Study B7841010 will be eligible to be enrolled in the global pivotal Phase 3 study, B7841005, unless a specific inclusion criterion is

			not met or an exclusion criterion is noted before Day 1 (Screening visit), of B7841005. (Section 2.2) • Added footnote to Table 3 to clarify that $t_{1/2}$, AUC_{inf}, CL/F and V_z/F will be reported if data permit. • Added detailed list of baseline variables. (Section 3.4) • Added description for "Physical Examination" in Safety Endpoints. (Section 3.5.5) • Added detailed reporting for ECG data, PT/INR, APTT, fibrinogen and ATIII activity. (Section 6.1) • Added detailed reporting for Max_{Eff} and AUEC with respect to PD endpoints. (Section 6.2.2) • Added subsections "Summary of Hemophilia History", "Summary of Bleeding Events" "Demographic and Clinical Examination Data", "Study Treatment Exposure" and "Concomitant Medications and Non-Drug Treatments" in Section 6.5. • Added Apendix 1: Categorical Classes for ECG and Vital Signs of Potential Clinical Concern; added Appendix 2: Clinically Laboratory, Vital Sign, and ECG Values.

2. INTRODUCTION

PF-06741086 is a human monoclonal immunoglobulin of the G isotype, subclass 1 (IgG1) that targets the Kunitz-2 domain of tissue factor pathway inhibitor (TFPI). PF-06741086 is in development as a prophylactic treatment to prevent or reduce the frequency of bleeding episodes in individuals with severe hemophilia A or B, with or without inhibitors.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7841010. 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, Endpoints, and Estimands

Table 2. Objectives and Endpoints

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

	area under the concentration-time curve from time 0 to infinity (AUC_{inf}), terminal half-life ($t_{1/2}$), apparent volume of distribution (V_z/F), apparent clearance (CL/F).
• To characterize the pharmacodynamic (PD) profile of a single SC dose of PF-06741086.	• TFPI (total and free); Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); Prothrombin fragment 1+2 (PF 1+2); D-dimer; Dilute prothrombin time (dPT); Day 1 up to Day 28.
• To characterize the immunogenicity of a single SC dose of PF-06741086.	• Frequency of anti-drug antibody (ADA) and neutralizing antibody (NAb) production against PF-06741086; Day 1 up to Day 28. Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay.

2.2. Study Design

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

Approximately 6 participants are planned for enrollment at 2 study sites. Participants who are withdrawn for any reasons may be replaced at the discretion of the investigator and after consultation with the sponsor. Participants will be screened within 35 days prior to administration of the investigational product to confirm that they meet the participant selection criteria for the study. Participants will be admitted into the Clinical Research Unit (CRU) 1 day prior to dosing (Day-1) and will accept a single SC injection of 300 mg PF-06741086 (150 mg *2) at Day 1. There is no dose modification plan during the study. Participants will be required to stay in the CRU through completion of the Day 7 evaluations. After that, it will be at investigator's discretion on whether the participants should stay in the CRU or not. All participants will return for weekly clinic visits on Day 14, Day 21 and Day 28 per the Schedule of Activities. The follow-up Visit at Day 42 could be a Phone Follow-Up visit or a face to face clinic visit at the discretion of the investigator. If Day 42 visit and the Screening visit of B7841005 occur on the same day, it must be an in- clinic visit.

Participants who experience a treatment-related adverse event (including lab abnormalities) at any time point will continue to be followed through resolution or stabilization of the event as agreed upon by the investigator and sponsor.

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

Participants who complete Study B7841010 will be eligible to be enrolled in the global pivotal Phase 3 study, B7841005, unless a specific inclusion criterion is not met or an exclusion criterion is noted before Day 1 (Screening visit), of B7841005.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Frequency, severity and causal relationship of TEAEs and withdrawals due to TEAE; Day 1 up to Day 42.
- Frequency and magnitude of abnormal laboratory findings (including hematology, PT/INR, APTT, chemistry, urinalysis, fibrinogen, ATIII activity and cTnI); Day 1 up to Day 28.
- Changes from baseline in vital signs (blood pressure, pulse rate, temperature and respiration rate) measurements, 12-lead ECG parameters and physical examination; Day 1 up to Day 28.
- Frequency, severity and causal relationship of injection site reactions; Day 1 up to Day 7.

3.2. Secondary Endpoints

3.2.1. Pharmacokinetic Endpoints

Plasma PF-06741086 concentrations as determined by a validated assay Day 1 up to Day 28, and noncompartmental PK parameters including C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, V_z/F, CL/F.

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

Table 3. Derivation of PF-06741086 Pharmacokinetic Parameters

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

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

a. If data permit.

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

3.2.2. Pharmacodynamic Endpoints

TFPI (total and free, "free" TFPI will only be analyzed if this assay is validated before the study completes"); Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); PF 1+2; D-dimer; dPT; Day 1 up to Day 28.

3.2.3. Immunogenicity Endpoints

Frequency of ADA and NAb production against PF-06741086; Day 1 up to Day 28. Only positive ADA samples and the corresponding baseline sample will be tested in the NAb assay.

3.3. Other Endpoints

None.

3.4. Baseline Variables

Baseline variables include,

- Medical history;
- Prior/concomitant medication;
- Physical examination;
- Demographics;
- Height and weight;
- Clinical laboratory tests;

- Vital signs;
- ECG parameters;
- ADA and NAb;
- PK concentration;
- PD endpoints: TFPI (total and free), dPT, PF1+2, D-dimer, thrombin generation (including lag time, peak thrombin generation, and endogenous thrombin generation potential).

Baseline is defined as the last pre-dose measurement except for ECG data. Baseline for ECG data will be defined as the average of triplicate ECG measurements collected prior to dosing on Day 1.

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event will be considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment regardless of whether a similar event of equal or greater severity existed in the baseline period.

3.5.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol. Baseline will be defined as the last pre-dose measurement.

Appendix 2 of the protocol lists clinical laboratory tests to be performed.

3.5.3. Vital Signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed at times detailed in the Schedule of Activities given in the protocol.

3.5.4. ECG Data

ECG will be collected as described in the protocol. Abnormal ECG findings (See Protocol Appendix 7) may be reported as adverse events.

3.5.5. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the the general appearance, the respiratory and cardiovascular systems, as well as participant reported symptoms.

3.5.6. Injection Site Reactions

Injection site reactions will be monitored for each subject from Day 1 to Day 7.

3.5.7. Other Safety Data

Additional safety data will be collected as described in the protocol and will be listed if collected in the sponsor's database.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Table 4. Analysis Sets

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

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

No formal hypothesis testing will be performed.

5.2. General Methods

Descriptive analyses will be performed.

For continuous variables, the data will be summarized using the number of subjects, mean, median, standard deviation, minimum, and maximum in accordance with current Pfizer's data and reporting standards. For appropriate PK and PD parameters, geometric mean and geometric coefficient of variation (geocv%) will also be summarized.

For categorical or ordinal variables, number of subjects, numbers and percentages of subjects meeting the categorical criteria will be supplied in accordance with current Pfizer's data and reporting standards.

5.3. Methods to Manage Missing Data

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

5.3.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations 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). For PK calculations, BLQ will be handled by the Pfizer standard processes. For PD calculations, BLQ values will be imputed as 0.5*LOQ in calculations.

5.3.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of mean and median profiles, statistics will be calculated having set concentrations to missing if one of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample).

2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

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

5.3.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a subject's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a subject discontinues).

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented with ≥50% evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter (due to any known error or event related to dosing or sample collection before all the compound is adequately

absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints (Safety Analyses)

All safety analyses will be performed on the safety population (as defined in Section 4).

Analysis of frequency, severity and causal relationship of AEs, TEAEs from Day 1 up to Day 42, and injection site reactions from Day 1 up to Day 7 will be provided. Changes from baseline in vital sign (blood pressure (BP), pulse rate, temperature and respiration rate) measurements and ECG parameters from Day 1 up to Day 28 will be summarized. Physical examination findings from Day 1 up to Day 28 will be listed. Frequency and magnitude of abnormal laboratory findings (including hematology, PT/INR, APTT, chemistry, urinalysis, fibrinogen, ATIII activity, and cTnI), ECG, BP, and pulse rate abnormalities from Day 1 up to Day 28 of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate, according to sponsor reporting standards.

For ECG data, the number of participants with uncorrected QT values >500 msec will be summarized. Listings of subjects with any single postdose value ≥500 msec will also be produced for QTcF. Numbers and percentages of subjects meeting the categorical criteria will be provided. All planned and unplanned measurements will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

Seperate analysis for PT/INR, APTT, fibrinogen, ATIII activity and cTnI will include:

- Descriptive summary including n, mean, median, standard deviation, geometric mean, geometric coefficient of variation (geocv%), minimum, and maximum, will be reported from Day 1 up to Day 28.

- Listing of abnormalities.

Analysis change from baseline for PT/INR, APTT, fibrinogen, ATIII activity and cTnI will include:

- Descriptive summary including n, mean, median, standard deviation, minimum, and maximum, will be reported from Day 1 up to Day 28.

6.2. Secondary Endpoints

6.2.1. Pharmacokinetic Analysis

6.2.1.1. Statistical analyses of PK Parameters

To assess the pharmacokinetics of PF-06741086, the PK parameters detailed in Section 3.2.1 will be listed and summarized for subjects in the PK Parameter Analysis Set (as defined in Section 4). Missing values will be handled as detailed in Section 5.3.

Descriptive summaries of PK parameters will include the set of summary statistics as specified in the table below.

Table 5. PK Parameters to be Summarized Descriptively

Parameter	Summary Statistics
AUC_{last}, AUC_{inf}, C_{max}, CL/F and V_Z/F	N, arithmetic mean, median, coefficient of variation (cv%), standard deviation, minimum, maximum, geometric mean and geometric coefficient of variation (geocv%).
T_{max}	N, median, minimum, maximum.
$t_{1/2}$	N, arithmetic mean, median, coefficient of variation (cv%), standard deviation, minimum, maximum.

There will be 1 summary table presenting all PK parameters.

6.2.1.2. Statistical analyses of PK Concentrations

Analysis for PF-06741086 concentrations from Day 1 up to Day 28 for subjects in the PK concentration analysis set (as defined in Section 4) will include:

- A listing of all concentrations sorted by subject ID, day, nominal time postdose, and actual times. Deviations from the nominal time will be given in a separate listing.
- A summary of concentrations by day and nominal time postdose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv%), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Median concentrations time plots (on both linear and semilog scales) against nominal time postdose.
- Mean concentrations time plots (on both linear and semilog scales) against nominal time postdose.
- Individual concentration time plots (on both linear and semilog scales) against actual time postdose.

The length of time used for the x-axes of these plots will be decided on review of the data, and will depend on how long PF-06741086 concentration is quantifiable above the limit of quantification in the matrix.

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

6.2.2. Pharmacodynamic Analysis

The PD parameters from Day 1 up to Day 28 detailed in Section 3.2.2 will be listed and summarized for subjects in the PD Parameter Analysis Set (as defined in Section 4).

Separate analysis for TFPI (total and free), dPT, PF1+2, D-dimer, and thrombin generation (parameters may include lag time, peak thrombin generation, and endogenous thrombin generation potential) for subjects in the PD analysis set (as defined in Section 4) will include:

- Descriptive summaries of PD endpoints by day and nominal time post dose, where the set of statistics will include n, mean, median, standard deviation, geometric mean, geometric coefficient of variation (geocv%) , minimum and maximum.
- Median pharmacodynamic endpoint time plots against sampling time.
- Mean pharmacodynamic endpoint time plots against sampling time.
- Individual pharmacodynamic endpoint time plots against sampling time.

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

Table 6. Other PD Parameters

Parameter	Definition	Method of Determination
Max_{Eff}	Maximum increase and decrease from baseline for free TFPI. Maximum increase from baseline for total TFPI, PF1+2, D-dimer, endogenous thrombin generation potential. Maximum decrease from baseline for dPT, thrombin generation lag time, peak thrombin generation.	Observed directly from data
AUEC	Area under the PD change from baseline-time profile from time zero to Day 28.	Linear/Linear trapezoidal method

The analysis of above parameters for subjects in the PD analysis set (as defined in Section 4) will include:

- Descriptive summary including n, mean, median, standard deviation, coefficient of variation (cv%), minimum, and maximum, will be reported.

6.2.3. Immunogenicity (ADA, NAb) Results

Immunogenicity (ADA, NAb) results from Day 1 up to Day 28 will be listed (including titers) by timepoint.

6.3. Other Endpoints

Not applicable.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Baseline variables will be summarized.

6.5.2. Study Conduct and Participant Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for safety analysis set.

Data will be reported in accordance with the sponsor reporting standards.

6.5.3. Summary of Hemophilia History

Number and percentage of subjects with Hemophilia A or Hemophilia B, with or without inhibitor, subjects with hemophilic arthropathy, as well as subjects with target joint (s) will be summarized.

6.5.4. Summary of Bleeding Events

Descriptive statistics of number of bleeding events (Day1-Day42) (n, mean, median, standard deviation, minimum and maximum) and bleeding type (spontaneous or traumatic) will be generated. In addition, number of bleeding events will also be summarized for hemophilia A and hemophilia B subjects separately, if applicable.

6.5.5. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index and height in accordance with the sponsor reporting standards.

6.5.6. Disposition(s)

How many patients completed the study, or discontinued with reasons will be detailed and summarized.

Data will be reported in accordance with the sponsor reporting standards.

6.5.7. Study Treatment Exposure

Study drug administration will be provided in a listing in accordance with the sponsor reporting standards.

6.5.8. Concomitant Medications and Non-Drug Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

6.6. Safety Summaries and Analyses

Adverse events, laboratory data, vital signs, ECG data, physical examination, injection site reactions and other safety data will be summarized in accordance with the sponsor reporting standards.

6.7. Additional Analyses to Address COVID-19 Pandemic Impacts

Protocol deviations related to COVID-19 pandemic will be listed.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analyses will be performed. This is an open-label single-arm study of exploratory nature. The sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK/PD modeling and supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. APPENDICES

Appendix 1. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

QTcF (ms)	450≤ max. <480	480≤ max.<500	max. ≥500
QTcF (ms) increase from baseline	30≤ max. <60	max. ≥60	

Categories for PR and QRS

PR (ms)	max. ≥300	
PR (ms) increase from baseline	Baseline >200 and max.	Baseline ≤200 and max. ≥50% increase
QRS (ms)	max. ≥140	
QRS (ms) increase from baseline	≥50% increase	

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Supine pulse rate (bpm)	min. <40	max. >120
Standing pulse rate (bpm)	min. <40	max. >140

Measurements that fulfill these criteria are to be listed in report.

Appendix 2. Clinically Laboratory, Vital Sign, and ECG Values

Hematology

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

Chemistry

Total bilirubin: >1.5 times the ULN

Direct bilirubin: >1.5 times the ULN

Indirect bilirubin: >1.5 times the ULN

Creatinine kinase: >2.0 times the ULN

Creatinine: >1.3 times the ULN

Cardiac Troponin I: >1.0 times the ULN

Coagulation Pathway

PT:	≥4 seconds above the baseline value
aPTT:	≥1.1 times the upper limit of normal
AntiThrombin III:	(ATIII) activity < lower limit of the reference range and ≥20% decrease from baseline
Fibrinogen:	≤0.5 times LLN or ≤0.5 times the baseline value

Vital Signs

Temperature:	>38.5°C		
Pulse Rate Supine/Sitting:	<40 or >120 BPM	Standing:	<40 or >140 BPM

Blood Pressure:	Systolic ≥30 mm Hg change from baseline in same posture Systolic <90 mm Hg
Diastolic:	≥20 mm Hg change from baseline in same posture Diastolic <50 mm Hg

Electrocardiogram

PR interval	≥300 msec
	≥1.25 times baseline when baseline >200 msec
	≥1.50 times baseline when baseline ≤200 msec
QRS interval	≥140 msec
	≥1.50 times baseline
QTcF interval	≥500 msec

Appendix 3. List of Abbreviations

Abbreviation	Term
ADA	antidrug antibodies
AE	adverse event
APTT	activated partial thromboplastin time
ATIII	anti-thrombin III
AUC	area under the curve
AUC_{inf}	area under the concentration-time curve from time 0 to infinity
AUC_{last}	area under the concentration time curve from time 0 to the time of the last quantifiable concentration
AUEC	area under the PD change from baseline-time profile from time zero to Day 28
BLQ	below the limit of quantitation
BP	blood pressure
CL/F	apparent clearance
C_{max}	maximum observed concentration
CRU	Clinical Research Unit
cTnI	cardiac troponin I
CV	coefficient of variation
dPT	dilute prothrombin time
ECG	electrocardiogram
FIX	coagulant factor IX
FVIII	coagulation factor VIII
geocv	geometric coefficient of variation
IgG1	immunoglobulin G isotype, subclass 1
INR	international normalized ratio
K_{el}	the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
LLQ	lower limit of quantification
NAb	neutralizing antibodies
NC	not calculated
ND	not done
NS	no sample
PD	pharmacodynamic(s)
PF 1+2	prothrombin fragment 1+2
PK	pharmacokinetic(s)
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
$t_{½}$	terminal half-life
T_{max}	time to reach maximum concentration

Abbreviation	Term
TEAE	treatment-emergent adverse events
TFPI	tissue factor pathway inhibitor
V_Z/F	apparent volume of distribution