PROTOCOL B7841002

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

STATISTICAL ANALYSIS PLAN

(SAP)

Version: 2.0

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7841002 is based on the protocol amendment 4 dated 02Oct2016.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Original Version
2	Section 2.1.1 and 2.2: editorial changes	To comply with Protocol Amendment 4.
	Section 3.1.2 and 6.5.2: removed reference to albumin: total globulin ratio.	Not applicable any more.
	Section 5.2.1 and 6.2.1.1: added presentation of model based ABR and its 80%CI, added SAS codes for generating these estimates.	To comply with the protocol.
	Section 6.1, 6.2 and 6.5.1: Added summary by dose level and hemophilia type	To comply with Protocol Amendment 4.
	Section 6.2: added Wilcoxon rank sum test for ABR	To provide sensitivity analysis.
	Section 6.4.2: changed summary of subject evaluation to by analysis set.	New CaPS format doesn't allow summary of these populations.
	Section 6.5.7: added definition and summary of clinical relevant NAb.	To provide more detailed analysis.

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.

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

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7841002. 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

2.1.1. Primary Objectives:

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

2.1.2. Key Secondary Objective

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

2.1.3. Secondary Objectives

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

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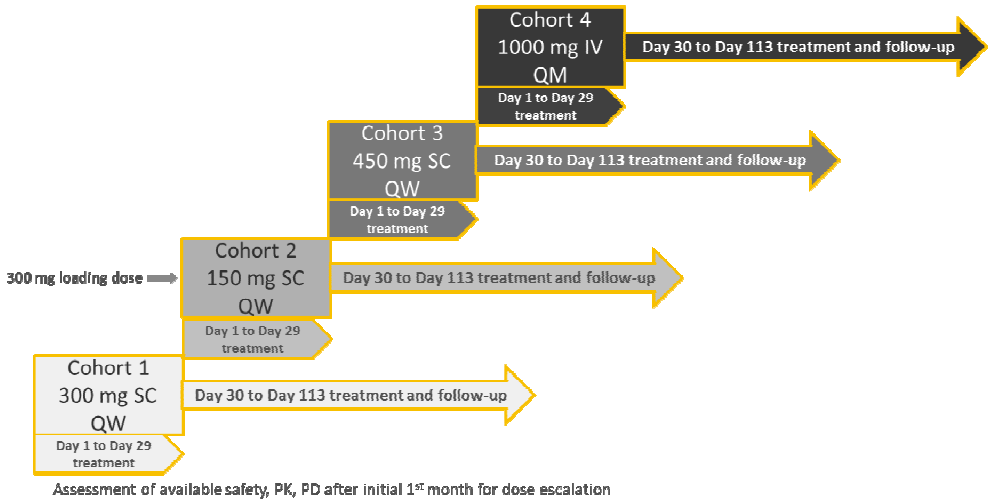
2.2. Study Design

B7841002 will be an open-label investigation of the safety, tolerability, PK, PD, and efficacy of multiple SC or IV doses of PF-06741086 in males with severe *hemophilia A or B. The subjects, investigator, site personnel, and Sponsor will not be blinded to the treatment assignment.*

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

Figure 1. Dose Escalation Scheme



SC/IV multiple dose cohorts will be enrolled in a dose-escalating fashion starting at the 300 mg SC dose. Subjects will be enrolled and assigned to treatment as follows:

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

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

Approximately 24 subjects are planned for enrollment at up to approximately 20 study sites. Subjects who are withdrawn for reasons other than safety may be replaced at the discretion of the Sponsor. Subjects with inhibitors to FVIII or FIX will be enrolled into cohorts currently open for enrollment. Additional subjects and/or cohorts may be enrolled in the event that the number of dosing cohorts or size of dosing cohorts is increased to fully define the dose range and/or clinical profile at the respective dose levels.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

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

- *Frequency and magnitude of abnormal laboratory findings (including hematology, PT/INR, aPTT, chemistry, urinalysis, fibrinogen, anti-thrombin III activity and cardiac troponin I); Day 1 up to Day 113.*

- *Changes from baseline in vital sign (blood pressure, pulse rate, temperature and respiration rate) measurements 12-lead electrocardiogram (ECG) parameters and physical examination; Day 1 up to Day 113.*

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

3.1.1. Adverse Events

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (applies to screening only) will not be counted as treatment emergent as this is a single-period study.

3.1.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol. In addition, total globulin will be derived as total protein(g/L)-albumin(g/L).

To determine if there are any clinically significant laboratory abnormalities, the hematological, clinical chemistry (serum) and urinalysis safety tests will be assessed against the criteria specified in the sponsor reporting standards. Laboratory parameters identified in Appendix 2 will also be assessed against criteria specified in that appendix. The respective assessments will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

Baseline will be the last pre-dose measurement.

3.1.3. Vital Signs

Single supine blood pressure and heart rate measurements will be taken at times detailed in the Schedule of Activities given in the protocol.

Baseline will be defined as the last pre-dose recording.

3.1.4. ECG

A single 12-lead ECG will be obtained on all subjects at screening. If ECG is abnormal, collect triplicate ECG. 12-lead ECGs will be recorded in triplicate for subjects on Day 1. On subsequent days, a single 12-lead ECG will be obtained on all subjects. If ECG is abnormal, collect triplicate ECG.

The QT interval, QTcF interval, PR interval, RR interval, QRS complex and heart rate will be recorded at each assessment time.

If not supplied, QTcF interval will be derived using Fridericia's heart rate correction formula: $QTcF = QT / (RR)^{1/3}$ where RR = 60/HR (if not provided)

The average of the triplicate readings will be calculated for each ECG parameter.

Baseline will be defined as the average of triplicate ECG measurements collected prior to dosing on Day 1.

3.1.5. Injection and Infusion Site Reactions

Injection and infusion site reactions will be monitored for each subject from Day 1 to Day 113.

3.1.6. 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.

3.2. Secondary Endpoints

3.2.1. Efficacy

- *Annualized rate of bleeding episodes; Day 1 up to Day 85.*

Baseline will be defined as the annualized bleeding rate during the 6 months prior to study enrollment.

3.2.2. Pharmacokinetics

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

3.2.3. Pharmacodynamics

- *Total TFPI; Day 1 up to Day 113.*
- *Thrombin generation (including lag time, peak thrombin generation and endogenous thrombin generation potential); Day 1 up to Day 113.*
- *Prothrombin fragment 1+2 (PF1+2); Day 1 up to Day 113.*
- *D-dimer; Day 1 up to Day 113.*
- *Dilute prothrombin time (dPT); Day 1 up to Day 113.*

Baseline will be defined as the last measurement prior to dosing on Day 1.

3.2.4. Immunogenicity

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

Formation of ADA and NAb will be monitored for each subject. Subjects with positive ADA or NAb may be required to attend additional, unscheduled follow-up visits after Day 113. Extended follow up visits every 2 weeks for up to 3 months, including vital signs, immunogenicity, AE and concomitant medication assessments, may be performed.

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3.4. Baseline Variables

Demographics, medical history, hemophilia history, including inhibitor status, target joint and hemophilic arthropathy and bleeding episodes over past 6 months, will be collected at screening visit.

4. ANALYSIS SETS

4.1. Full Analysis Set

In general, the full analysis set is comprised of all enrolled subjects. This population of subjects is not applicable for this study. Analysis sets for efficacy, PK, pharmacodynamic and safety data are defined in Section 4.3, Section 4.4, Section 4.5 and Section 4.2.

4.2. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

4.3. Per Protocol Analysis Set

The Per Protocol Analysis Set (PPAS) will be a subset of the Safety Analysis Set. This set will exclude subjects with major protocol deviations.

Major protocol deviations include but not limited to:

- Lack of compliance in study drug administration;
- Violations on concomitant medications, see Protocol Section 5.7.1.

The full list of protocol deviations will be reviewed prior to database lock and a decision will be taken regarding exclusion from the PPAS.

4.4. Pharmacokinetic Analysis Set

Subjects who experience events that may affect their PK profile may be excluded from the PK analysis. At the discretion of the Clinical Pharmacologist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

4.4.1. Concentration Analysis Set

The PK concentration population is defined as all enrolled subjects treated who have at least 1 quantifiable concentration.

4.4.2. PK Parameter Analysis Set

The PK parameter analysis population is defined as all enrolled subjects treated who have at least 1 of the PK parameters (detailed in Section 3.2.2).

4.5. Pharmacodynamic Analysis Set

The pharmacodynamic analysis population is defined as all enrolled subjects who receive at least 1 dose of study medication and have a baseline measurement and at least 1 post-dose measurement for at least 1 PD endpoint (detailed in Section 3.2.3).

4.6. Other Analysis Sets

None.

4.7. Treatment Misallocations

All analyses will be performed on an "as-treated" basis and will not include data from subjects who are enrolled but not treated.

If a subject takes a treatment that is not consistent with the treatment they are assigned to, for example takes a treatment out of cohort, then they will be reported under the treatment that they actually receive for all efficacy, safety, PK and pharmacodynamic analyses, where applicable.

4.8. Protocol Deviations

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure. Subjects with major protocol deviations may be excluded from an analysis population, as appropriate.

4.8.1. Deviations Assessed Prior to Treatment Assignment

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.

4.8.2. Deviations Assessed Post-Treatment Assignment

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis will be performed at study subject data set release after LSLV.

5.1. Hypotheses and Decision Rules

Prophylactic treatment with PF-06741086 will be considered superior to On Demand treatment with respect to ABR reduction if 1) the upper limit of the 2-sided 80%CI of the ratio of ABR in PF/historical On Demand is <1 and 2) the estimate of the ratio of ABR in PF/historical On Demand $\leq$0.3. Drug will be considered not superior to On Demand treatment if the lower limit of the 2-sided 80%CI of the ratio of PF/historical On Demand >0.3.

The primary efficacy endpoint in the four dose cohorts will be tested in a hierarchical order to control the overall family-wise error rate. The efficacy test will first be performed in the dose cohort with the highest PK exposure (eg, C_{trough} and/or AUC) that is proven to be safe and tolerated. If the result is significant, the ABR will be tested against the historical On Demand group in the dose cohort with the next highest PK exposure. The test procedure will continue until the dose cohort with the lowest PK exposure is tested against the historical On Demand group.

5.2. General Methods

5.2.1. Analyses for Continuous Data

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

5.2.2. Analyses for Categorical Data

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.

5.2.3. Analyses for Count Data

Separate models will be run for each pairwise comparison between the historical control group and each dose cohort. The frequency of bleedings will be analyzed using a negative binomial model. Log transformed duration of time on study will be included as an offset variable in the model.

Sample SAS codes are provided as follows:

```
PROC GENMOND Data=sample;
        Where dose='300mg SC';
        Class trt;
        Model count=trt/dist=negbin link=log offset=logtime alpha=0.2 ;
        Estimate 'PF-06741086 - PCB' trt 1 -1;
        Estimate 'PF-06741086' intercept 1 trt 1/alpha=0.2;
        ods output ParameterEstimates=pvalue estimates=est;
Run;
```

5.2.4. Mixed Model Repeated Measures (MMRM)

Change from baseline of each PD endpoint will be analyzed using a mixed model for repeated measures (MMRM) with a restricted maximum likelihood method for the estimation of the covariance parameters. The model will include dose, study day and dose by study day interaction as fixed categorical effects as well as baseline value as a fixed effect continuous covariate. Subject will also be included in the model as a random effect. An unstructured covariance matrix will be used to model the within-subject errors. If model fitting issues occur with the unstructured covariance matrix, other covariance structures including Toeplitz, compound symmetry, and autoregressive (1) will be considered. The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used as the primary analysis: the competing models will be ranked according to their AIC, with the one having the lowest AIC being the best. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

5.3. Methods to Manage Missing Data

5.3.1. Safety Endpoints

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

5.3.2. PK Endpoints

5.3.2.1. 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.

5.3.2.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of 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.

5.3.2.3. 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 for a particular dose with ≥50% evaluable measurements.

If an individual subject has a known biased estimate of a PK parameter, this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.3. PD Endpoints

Analysis of PD endpoints using mixed model repeated measures (MMRM) makes the

assumption that the data are "missing at random (MAR)" and utilizes all relevant partial data obtained from a subject without requiring a specific imputation of missing values.

5.3.4. Efficacy Endpoint

Missing data will not be imputed.

6. ANALYSES AND SUMMARIES

6.1. Primary Safety Endpoint(s)

A set of summary tables split by dose level and cohort will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06741086. In addition, if data permits, summary tables will also be presented for hemophilia A and hemophilia B subjects separately. Diagnosis of hemophilia A or B will be derived based on Factor VIII activity or Factor IX activity level (≤1%) respectively at screening.

No formal analyses are planned for safety data. The safety and other endpoints detailed in Section 3.1 will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the Safety Analysis Set (as defined in Section 4.2). The details are provided in Section 6.4.6.

6.2. Secondary Endpoint(s)

6.2.1. Efficacy Endpoint

6.2.1.1. Statistical Analysis

The efficacy analysis will be conducted in the PPAS. A historical On Demand group will be constructed using the following internal Pfizer studies: ReFacto AF 3082B2-4432 (B1831004), BeneFIX B1821010, and BeneFIX 3090A1-400 (B1821004). Subjects who are on On Demand treatment in B1831004, as well as data from the On Demand period in B1821004 and B1821010 will be used to construct the historical On Demand group. The resulting dataset will be further filtered to match the key inclusion/exclusion criteria of B7841002 based on age and factor activity ($18 \leq$ age ≤ 65 and factor activity $\leq 1\%$). Outliers with extremely high ABR will be removed from the pooled On Demand group, if appropriate. All resulting subjects will be included in the historical control group.

The frequency of bleedings will be analyzed using a negative binomial model as detailed in Section 5.2.3. The ratio of ABR and its 80% 2-sided CI in the PF-06741086 arm versus that in the historical On Demand group will be generated for each dose cohort. The corresponding p-value will also be presented. Model based ABR and its 80%CI will be generated for each dose cohort.

6.2.1.2. Descriptive Summary

Descriptive statistics of ABR (n, mean, median, standard deviation, minimum and maximum) will be generated by dose level and cohort for both the treatment period and the 6 months prior to study enrolment. ABR from the historical On Demand group will also be presented. It may take time for the inflammation in the joints to settle, and thus the number of bleeding episodes during the first month post-dose may be higher than the last two months on drug. In order to investigate whether the ABR decreases over time, the ABR in the PF-06741086 arm will be summarized by study month and dose level and cohort. Two bar graphs will be generated presenting mean and median ABR by study month, respectively. The ABR during the 6 months prior to study enrolment will be plotted together with the on-study ABR. All dose cohorts as well as the historical On Demand group will be presented on the same plot.

In addition, ABR will also be summarized for hemophilia A and hemophilia B subjects separately, if applicable.

If the analysis of PD biomarker data shows that with increasing dose levels, the PD effect reaches plateau, ABR from different dose levels may be pooled together and analyzed against the historical On Demand group.

6.2.1.3. Sensitivity Analysis

An exact Wilcoxon-rank sum test will be utilized to test the difference in ABR between active treatment and historical On Demand group. A one sided p-value <0.1 will be considered as statistically significant. The same hierarchical approach as described in Section 5.1 will be used for multiplicity control.

6.2.2. Pharmacokinetic Endpoints

PK parameters for PF-06741086 will be listed and summarized for subjects in the PK Parameter Analysis Set (as defined in Section 4.4.2) by dose level and cohort and study day as shown in the following table:

Table 2. PK Parameters to be Summarized Descriptively for PF-06669571 and L-DOPA by Day

Dose	Parameter	Summary Statistics
Single Dose (Day 1 to Day 7 QW or Day 1 to Day 28 QM)	AUC_{last}, C_{168h} (Day 1 to Day 7 QW), C_{672h} (Day 1 to Day 28 QM), C_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
Single Dose (Day 1 to Day 7 QW or Day 1 to Day 28 QM)	T_{max}	N, median, minimum, maximum.
Multiple Dose (Day 29 to Day 36 (QW) or Day 29 to Day 57 (QM))	$C_{max, ss}$, AUC_{τ}, V_{ss} (for IV administration only), CL (for IV administration only), CL/F (for SC administration only), C_{min}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
Multiple Dose (Day 29 to Day 36 (QW) or Day 29 to Day 57 (QM))	$T_{max, ss}$	N, median, minimum, maximum.

There will be 1 summary table presenting all PK parameters. This will include data from both routes of administration. The treatment subheading will include the route of administration and dose information.

6.2.2.1. Statistical analyses of PK Concentrations

Presentations for PF-06741086 concentrations for subjects in the Concentration Analysis Set (as defined in Section 4.4.1) will include:

- A listing of all concentrations sorted by dose level and cohort, subject ID, day, nominal time post-dose, and actual times. Deviations from the nominal time will be given in a separate listing;

- A summary of concentrations by dose level and cohort, day and nominal time post-dose, 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 semi-log scales) against nominal time post-dose by dose (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose);

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by dose level and cohort (all doses on the same plot per scale, based on the summary of concentrations by dose and time post-dose);

- Individual concentration time plots by dose level and cohort (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each dose per scale).

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.

6.2.3. Pharmacodynamic Endpoints

Endpoints:

- Total TFPI;

- Thrombin generation (lag time, peak thrombin generation, and endogenous thrombin generation potential);

- PF1+2;

- D-dimer;

- dPT;

- Analysis time window: Day 1 up to Day 113;

- Analysis population: Pharmacodynamic Analysis Set (defined in Section 4.5);

- Analysis methodology: Change from baseline will be analyzed using the MMRM model (detailed in Section 5.2.4). Change from baseline will also be analyzed using a four parameter Emax model. The detailed Emax modeling will be described in a separate PK/PD plan. Subjects with detectable FVIII activity (hemophilia A) or FIX activity (hemophilia B) at the time of a PD specimen collection may have result(s) for the respective PD parameter censored from the PD analysis.

Reporting results:

- Raw data: For each endpoint of interest, the number of subjects, mean, median, standard deviation, geometric mean, geometric coefficient of variation (cv%), minimum, and maximum, will be summarized by dose level and cohort and study day;

- Change from baseline: the number of subjects, mean, median, standard deviation, geometric mean, geometric coefficient of variation (cv%), minimum, and maximum, will be summarized by dose level and cohort and study day. Baseline is defined in Section 3.2.3. The model based mean and 80% two sided CI will be presented by dose level and cohort and study day.

Figures:

- Median pharmacodynamic endpoint time plots against study day by dose level and cohort (all doses on the same plot, based on the summary of pharmacodynamic endpoint by dose and study day). The plot will be generated for absolute value as well as the change from baseline value. Two sets of plots will be produced, with the x-axis being on nominal and semi-log scales, respectively.

- Mean pharmacodynamic endpoint time plots against study day by dose level and cohort (all doses on the same plot, based on the summary of pharmacodynamic endpoint by dose and study day). The plot will be generated for absolute value as well as the change from baseline value. Two sets of plots will be produced, with the x-axis being on nominal and semi-log scales, respectively.

- Individual pharmacodynamic endpoint time plots against study day by dose level and cohort (there will be separate spaghetti plots for each dose). The plot will be generated for absolute value as well as the change from baseline value.

- The model based mean and 80% two sided CI from the MMRM model will be plotted against study day. All dose cohorts will be presented on the same plot with one line representing one dose cohort.

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6.4. Baseline and Other Summaries and Analyses

6.4.1. Summary of Hemophilia History

Number and percentage of subjects with Hemophilia A or Hemophilia B, subjects with hemophilic arthropathy, as well as subjects with target joint (s) will be summarized by dose

level and cohort and overall. Historical ABR during the 6 months prior to screening will be summarized descriptively by dose level and cohort.

6.4.2. Study Conduct and Subject Disposition

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for each analysis set. Frequency counts will be supplied for subject discontinuation(s) by dose cohort.

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

6.4.3. 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.

6.4.4. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by dose cohort.

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

6.4.5. Study Treatment Exposure

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

6.4.6. Concomitant Medications and Non-Drug Treatments

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

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

Adverse events (AEs) will be reported in accordance with the sponsor reporting standards. AEs will also be summarized separately by inhibitor status, if applicable.

In addition, thrombotic events will be listed and summarized by dose level and cohort if data permits. A list of thrombotic events is provided in Appendix 1 of the protocol. If the subject has received concomitant administration of a bypass agent (ie, NovoSeven, NovoSeven RT, Niastase, eptacog alfa, FEIBA, Activated prothrombin complex concentrate, APCC, anti-inhibitor coagulant complex concentrate) at the onset of a thrombotic event, the type and dose of bypass agent will be presented as well.

6.5.2. Laboratory Data

Laboratory data (including total globulin, PT/INR, aPTT, fibrinogen, anti-thrombin III and cardiac troponin I) will be listed and summarized by dose level and cohort in accordance with the sponsor reporting standards. Baseline is as defined in Section 3.1.2. In addition, laboratory parameters identified in the appendix 2 of the study protocol will be summarized categorically against criteria specified in that appendix. The respective assessments will take into account whether each subject's baseline test result is within or outside the laboratory

reference range for the particular laboratory parameter. Two sets of summaries will be generated: one for subjects with normal baseline value and one for subjects with abnormal baseline value.

6.5.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by dose level and cohort and study day, according to sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.3.

The maximum increase from baseline for supine systolic, diastolic blood pressures and pulse rate will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

Similarly, the maximum decrease from baseline for supine systolic, diastolic blood pressures and pulse rate will be determined by selecting the minimum value of the changes from baseline. In cases where a subject does not show a decrease, the minimum increase should be taken.

Maximum absolute values and changes from baseline for vital signs will also be summarized descriptively by dose level and cohort using categories as defined in Appendix 1. 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.

Maximum increases and decreases in vital signs will be summarized by dose level and cohort according to sponsor reporting standards.

6.5.4. Electrocardiogram

Absolute values and changes from baseline in QT, heart rate, QTcF, PR, RR and QRS will be summarized by dose level and cohort and study day using sponsor reporting standards. Tables will be paged by parameter. Baseline is as defined in Section 3.1.4.

The maximum absolute value (post-dose) and the maximum increase from baseline for QT, heart rate, QTcF, PR, and QRS will be determined over all measurements taken post-dose.

The maximum increase from baseline will be calculated by first subtracting the baseline value from each post-dose measurement to give the change from baseline. The maximum of these values over the respective period will then be selected, except in the case where a subject does not show an increase. In such an instance, the minimum decrease should be taken.

Maximum increase from baseline for QT, heart rate, QTcF, PR and QRS will be summarized by dose cohort, according to sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by dose level and cohort and study day using categories as defined in Appendix 1 (for QTc these correspond to ICH E14).[1] 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.

Listings of subjects with any single postdose value ≥500 msec will also be produced for QTcF.

6.5.5. Physical Examination

Physical exam results will be provided in a data listing in accordance with the sponsor data reporting standard.

6.5.6. Injection and Infusion Site Reactions

The frequency of injection and infusion site reactions will be summarized and listed by dose level and cohort, according to sponsor reporting standards.

6.5.7. Other Safety Data

6.5.7.1. Immunogenicity

The immunogenicity results will be generated according to the sponsor's standard reporting standards, including:

- Summary of ADA and NAb analysis by sample;
- Summary of ADA and NAb analysis by subject;
- Summary of incidence of ADA and NAb by dose level and cohort and study day;
- Individual plots of PK concentration against time by dose level and cohort, ADA or NAb positive subjects will be denoted by a different color or symbol versus the ADA or NAb negative subjects;
- Individual plots of PD endpoints (as defined in Section 3.2.3) against time by dose level and cohort, ADA or NAb positive subjects will be denoted by a different color or symbol versus the ADA or NAb negative subjects;
- Listing of indicidual level ADA and Nab incidence (clinically relevant NAb will be denoted);
- Listing of individual ABR by ADA and NAb status, separated by dose cohort.

In addition to the above standard outputs, the incidence of clincially relevant NAb will be summarized similarly as ADA and NAb, where clinically relevant is defined as a) treatment emergent Nab immune response present on ≥2 determinations and b) loss of PD effect (return to baseline) after previous demonstration of PD effect (in that subject) for at least 2 of the PD

parameters (total TFPI, PF1+2 and peak thrombin by Thrombin Generation Assay) during active treatment period. "Return to Baseline" is defined as follows: if the observed post baseline PD measurement falls within the two-sided 95%CI band of the baseline measurement after previous demonstration of PD effect (in that subject), then it is said that the PD measurement returns to baseline.

7. INTERIM ANALYSES

Cumulative data will be reviewed for dose escalation as defined in Protocol Section 3.2. The safety, PK, PD and efficacy data will be routinely reviewed by the study team for internal decisions regarding future study planning. Additional cohort(s) may be added, and a cohort may be expanded to fully explore the dose range and/or efficacy endpoint following the review of the cumulative data.

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

8. REFERENCES

1. ICH E14 - The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04.

9. 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 Significant 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 or ≤0.77 times the baseline value if the baseline result is less than the lower limit of the reference range.

Chemistry

Total bilirubin: >1.5 times the ULN

Direct bilirubin: >1.5 times the ULN

Indirect bilirubin: >1.5 times the ULN

Creatinine kinase: >2.0 times the ULN

Creatinine: >1.3 times the ULN

Coagulation Pathway

PT:	≥4 seconds above the limits of the reference range
Cardiac Troponin I: ischemia range	If values are normal at baseline, any results above the myocardial
	Any result in the myocardial infarction range, regardless of baseline values
Fibrinogen:	≤0.5 times LLN or ≤0.5 times the baseline value

Vital Signs

Temperature:	>38.5°C
Pulse Rate Supine/Sitting:	<40 or >120 BPM Standing: <40 or >140 BPM
Blood Pressure: <90 mm Hg	Systolic ≥30 mm Hg change from baseline in same posture Systolic

Diastolic: Hg	≥20 mm Hg change from baseline in same posture Diastolic <50 mm

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