PROTOCOL B7841003

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

STATISTICAL ANALYSIS PLAN

(SAP)

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7841003 is based on the protocol dated 17Apr2017.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Original Version

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 B7841003 is a long-term study on the safety, tolerability and efficacy of PF 06741086 during 6 months of continuous treatment. Data on bleeding events will be collected to evaluate the therapeutic efficacy of prophylaxis with PF-06741086. Satisfactory safety, tolerability, and efficacy data from this study are intended to support the development of PF 06741086 as a treatment in hemophilia.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B7841003. 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 long-term treatment (continuous 6 months) with PF-06741086 in severe hemophilia A and B subjects.*

2.1.2. Secondary Objectives

- *To determine the efficacy of long-term treatment with PF-06741086 in severe hemophilia A and B subjects.*

2.1.3. Exploratory Objectives

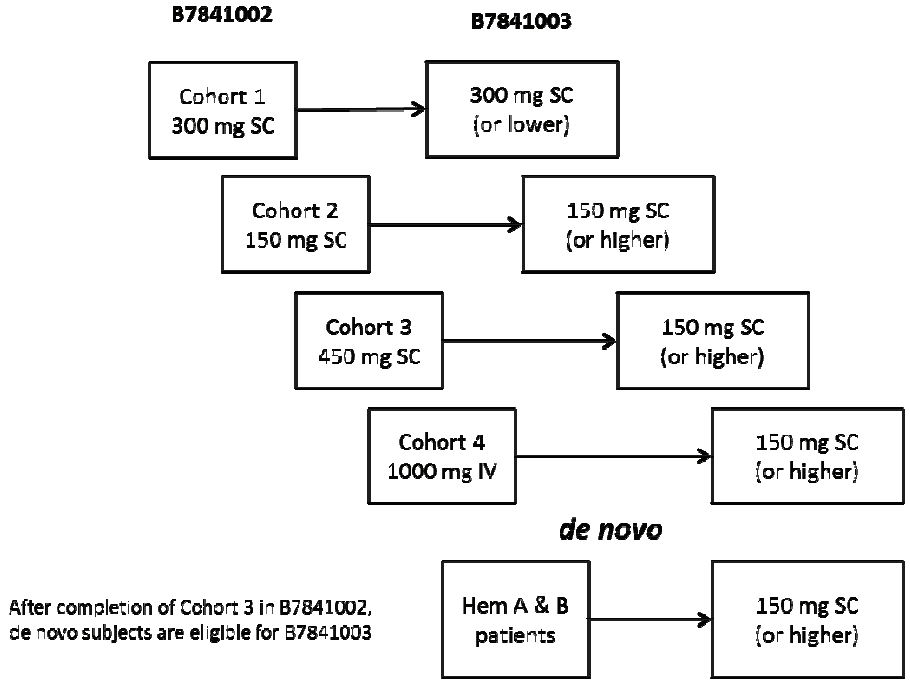
- [redacted]
- [redacted]
- [redacted]

[redacted]

2.2. Study Design

B7841003 is an open-label long-term (continuous treatment of 6 months or more) evaluation of PF-06741086 as a prophylactic regimen in subjects with hemophilia A or B. Investigators, subjects, site staff and Sponsor study team members will not be blinded to treatment assignment. Subjects will be assigned to treatment cohorts as indicated in Figure 1 below.

Figure 1. B7841003 Dose Assignment



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

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

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

Approximately 36 subjects (24 subjects from B7841002 and 12 additional de novo subjects) are planned for enrollment at approximately 20 study sites. Subjects who are withdrawn for reasons other than safety may be replaced at the discretion of the Sponsor.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- *Frequency, severity and causal relationship of treatment emergent adverse events (TEAEs); Day 1 up to Day 197.*
- *Frequency and magnitude of abnormal laboratory findings (including hematology, chemistry, urinalysis); Day 1 up to Day 197.*
- *Changes from baseline in vital sign (blood pressure, pulse rate, temperature and respiration rate) measurements and physical examinations; Day 1 up to Day 197 and ECG Day 1 to Day 29 in de novo subjects only.*
- *Frequency, severity and casual relationship of infusion and injection site reactions; Day 1 up to Day 197.*

3.1.1. Adverse Events

For subjects who roll over from B7841002, events that occur in the screening period will not be counted as treatment emergent in B7841003. Only events occurring following start of treatment in B7841003 will be counted as treatment emergent in the B7841003 study.

For de novo subjects, any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

3.1.2. Laboratory Safety Tests

Safety laboratory tests will be performed as described in the protocol.

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. 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 in B7841003. This baseline is denoted as "B7841003 baseline". An overall baseline is defined as the pre-dose measurement on Day 1 in B7841002 for rollover subjects.

3.1.3. Vital Signs

Single supine blood pressure, pulse rate, temperature and respiration 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 in B7841003.

3.1.4. ECG

ECG will be collected in de novo subjects only, at Screening, on Day 1 and Day 29 according to the Schedule of Assessments. A single 12-lead ECG will be obtained at screening. If ECG is abnormal, collect triplicate ECG. 12-lead ECGs will be recorded in triplicate on Day 1. On Day 29, a single 12-lead ECG will be obtained. 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 in B7841003.

3.1.5. Injection and Infusion Site Reactions

Injection and infusion site reactions will be monitored for each subject from Day 1 to Day 197.

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

- *Frequency and annualized rate of bleeding episodes; Day 1 up to Day 197.*
- *Frequency of rescue (FVIII, or FIX or bypass agent) therapy for treatment of breakthrough bleeding episodes.*

The annualized bleed rate (ABR) during the 6 month prior to study participation (for de novo subjects: 6 months prior to participation in B7841003; for roll over subjects: 6 months prior to participation in B7841002) will be collected and presented as baseline.

Baseline is not defined for frequency of rescue therapy.

3.3. Exploratory Endpoints

[redacted]

[redacted]

3.4. Baseline Variables

For de novo subjects, medical history, hemophilia history, including inhibitor status, target joint and hemophilic arthropathy, will be collected at screening visit. For roll over subjects, medical history, including target joint and hemophilic arthropathy will be collected in the B7841002 study.

4. ANALYSIS SETS

4.1. Full Analysis Set

In general, the full analysis set is comprised of all randomized subjects. This population of subjects is not applicable for this study.

4.2. Safety Analysis Set

All subjects who receive at least 1 dose of study medication in B7841003 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.

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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 randomized but not treated.

If a subject takes a treatment that is not consistent with the treatment they are randomized 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, CCI 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.

4.8.1. Deviations Assessed Prior to Randomization

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-Randomization

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

No formal hypothesis testing and decision rules will be performed.

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. CCI

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.

5.3. 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.

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5.3.3. Efficacy Endpoint

Missing data will not be imputed.

6. ANALYSES AND SUMMARIES

6.1. Primary Safety Endpoint(s)

A set of summary tables by dose level and cohort will be produced to evaluate any potential risk associated with the safety and tolerability of long-term administeration of PF-06741086. If data permits, separate summary tables will be provided by hemophilia type (hemophilia A or hemophilia B). A sample table is provided below:

Sample Summary Table

B7841002-B7841003 Dose	300mg-300mg SC QW non-inhibitor	150mg- XX mg SC QW	450mg-XX mg SC QW	300 mg–XX mg SC QW inhibitor	de novo cohort 1 (XX mg SC QW)	de novo cohort 2 (XX mg SC QW)	Overall-300mg SC QW	Overall-XXmg SC QW
Mean								
SD								
Median								
Min								
Max								
n								

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 6.6.

6.2. Efficacy Endpoint(s)

The efficacy analysis will be conducted in the Per Protocol Analysis Set.

Descriptive statistics of ABR (n, mean, median, standard deviation, minimum and maximum) during the course of B7841003 will be generated by cohort and dose level. The representation of the summary table will follow the sample table as shown in Section 6.1. If data permits, ABR will also be summarized separately by hemophilia type following the same table format. In addition, ABR data from B7841003 will also be pooled with data from B7841002 to evaluate the long term effect of PF-06741086.

Frequency of rescue therapies (including factor concentrate for non-inhibitor subjects and bypassing agent for inhibitor subjects) during the course of B7841003 will be summarized similarly as the ABR endpoint.

The above analyses will be conducted in the Safety Analysis Set as a sensitivity analysis as well.

6.3. Exploratory Endpoints

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6.5. Baseline and Other Summaries and Analyses

6.5.1. 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 cohort that the subjects are enrolled in B7841002, dose level and overall. Diagnosis of hemophilia A or B will be derived based on Factor VIII activity or Factor IX activity level (≤1%) respectively at screening. Historical ABR during the 6 months prior to screening will be summarized descriptively.

6.5.2. 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 cohort and dose level.

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

6.5.3. 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.

6.5.4. Discontinuation(s)

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

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

6.5.5. Study Treatment Exposure

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

6.5.6. Concomitant Medications and Non-Drug Treatments

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

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards.

In addition, thrombotic events (TE) will be listed and summarized if data permits. A list of thrombotic events is provided in Appendix 2 of the protocol. The listing will also present the dose level of PF-06741086 the subject is on when the thrombotic event occurs. If the subject is also on bypassing agent at the time of developing thrombotic event, the type and dose of bypassing agent will be presented as well. The incidence of TE per patient-month of observation, as well as it's 90%CI will be calculated and presented by cohort and dose level.

6.6.2. Laboratory Data

Laboratory data (including PT/INR, aPTT, fibrinogen, anti-thrombin III and cardiac troponin I) will be listed and summarized by cohort and dose level in accordance with the sponsor reporting standards. Summaries will be provided with regard to B7841003 baseline. For roll over subjects, a second set of summaries will be provided regarding to the overall baseline by subgroup (defined in Section 3.3). 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.

6.6.3. Vital Signs

Absolute values and changes from baseline in supine systolic and diastolic blood pressure and pulse rate will be summarized by cohort, dose level 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 and diastolic blood pressures 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 and diastolic blood pressures 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 cohort and dose level 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 cohort and dose level according to sponsor reporting standards.

6.6.4. Electrocardiogram

Absolute values and changes from baseline in QT, heart rate, QTcF, PR, RR and QRS will be summarized by dose level 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 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.

6.6.5. Physical Examination

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

6.6.6. Injection and Infusion Site Reactions

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

7. INTERIM ANALYSES

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 CCI *, 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.

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. ≥25% increase	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.