Pfizer Inc

C0371005

Gene therapy, open-label, dose-escalation study of PF-06838435 (SPK-9001) [adeno-associated viral vector with human factor IX gene] in subjects with hemophilia B

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Statistical Analysis Plan

Version 4.0

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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

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List of Abbreviations

AAV	Adeno-associated virus vector
ABR	Annualized bleed rate
AIR	Annualized infusion rate
AE	Adverse event
aPTT	Activated partial thromboplastin time
BMI	Body mass index
CRF	Case Report Form
DNA	Deoxyribonucleic acid
EHL-rFIX	Extended half-life recombinant factor IX
ELISPOT	Enzyme-linked immunospot assay
EOS	End of study
FIX	Coagulation factor IX
FIX:C	Factor IX in circulation
HAL	Hemophilia activities list
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hFIX	Human coagulation factor IX
HIV	Human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HRQoL	Health-related quality-of-life
ICF	Informed consent form
INR	International normalized ratio
IU	International unit
LFT	Liver function test
LLN	Lower limit of Normal
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
PBMC	Peripheral blood mononuclear cells
pd-FIX	Plasma-derived factor IX
PK	Pharmacokinetics
PT	Preferred term
rFIX	Recombinant factor IX
RNA	Ribonucleic acid
ROTEM	Rotational thromboelastogram
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SPK-9001	AAV-Spark100-hFIX39- Padua. Adeno-associated viral vector comprised of the AAV-Spark100 capsid, and a codon-optimized FIX mini-gene encoding human FIX-Padua under control of the human α1-antitrypsin promoter coupled to the human apolipoprotein E hepatic locus control region

TAT	Thrombin-antithrombin
TEAE	treatment-emergent adverse events
TEG	Thromboelastography
TGA	Thrombin generation assay
ULN	Upper limit of normal
VAS	Visual analogue scale
WHO	World Health Organization

1. Introduction

Hemophilia B, or Christmas disease, is a rare congenital bleeding disorder characterized by the deficiency of blood coagulation factor IX (FIX). Individuals with hemophilia B often experience mild-to-severe bleeding complications and it can be life-threatening if not treated appropriately. There is no available cure for hemophilia B. Prophylaxis, with regular infusion of FIX concentrates, is now the mainstay of hemophilia care to resolve bleeding episodes (episodic treatment) or prevention of bleeding (prophylaxis treatment) (Roberts and Eberst 1993; Srivastava et al. 2012; National Hemophilia Foundation 2007).

Over the past two decades, a series of preclinical and early-phase clinical studies on gene transfer for hemophilia have demonstrated a good safety profile using adeno-associated viral (AAV) for hemophilia B. Recent success reported by Nathwani et al., (2011 and 2014) of sustained long-term expression (up to 6 years) of therapeutic levels of FIX between 2% and 6% activity levels in subjects with severe hemophilia B using AAV serotype 8 (AAV8) liver-directed gene transfer further validated the potential of gene transfer technology.

PF-06838435 is an adeno-associated viral (AAV) vector expressing the human factor IX-Padua (hFIX-Padua) variant. PF-06838435 is being administered for the first time to humans; however, AAV vectors have been administered to humans in more than 100 gene therapy clinical trials for a wide range of indications, including hemophilia B (Nathwani et al. 2014; Buchlis et al. 2012; Mingozzi and High 2013; Mingozzi and High 2011b; High and Aubourg 2011).

Protocol number was changed to C0371005 (formerly SPK-9001-101) after Investigational New Drug (IND) transfer from Spark Therapeutics to Pfizer Inc on July 11, 2018.

2. Objectives

2.1. Primary and Secondary Objectives

The primary objective of the study is to evaluate the safety and tolerability of a single intravenous infusion of PF-06838435 in hemophilia B subjects ≥18 years of age with ≤2 IU/dL [≤2 %] endogenous factor IX [FIX]). The secondary objective is to characterize the kinetics of PF-06838435.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 1/2a, open-label, non-randomized, dose-escalation and multi-center study to evaluate the safety, tolerability, and kinetics of a single intravenous infusion of PF-06838435 in hemophilia B subjects with ≤2IU/dL [≤2%] endogenous factor IX [FIX]).

Approximately 15 evaluable subjects will be dosed with a single intravenous infusion of PF-06838435 at one of three different dose levels.

Subjects will provide informed consent and then undergo screening assessments up to 6 (±2) weeks prior to PF-06838435 infusion on the Dosing Day (Day 0). All dosed subjects will undergo safety observation for a total of 52 (±2) weeks after PF-06838435 infusion(see the Schedule of Events). Subjects who complete 52 (±2) weeks (End-of-Study) will be encouraged to enroll in an extension study evaluating the long-term safety of PF-06838435 for up to an additional 5-year long-term follow-up (LTFU).

The administration of PF-06838435 to the first two subjects in the starting dose level will be staggered by at least two (2) weeks to ensure safety. Additionally, at least eight weeks of safety data from at least three (3) out of five (5) subjects in a given dose level will undergo review by an independent Data Monitoring Committee (DMC) prior to dosing the first subject in the next dose level.

There will be no dose escalation if at least three (3) subjects in any dose level achieve steady-state vector-derived FIX activity levels of ≥40%. Steady-state levels are based on an average of vector-derived FIX:C activity level measurements starting from Week 12 with adequate washout (i.e., 96 hours for pd- or r-FIX and up to 168 hours for extended half-life rFIX) from FIX product.

Originally, up to five (5) evaluable subjects may be dosed in each dose level. An initial dose level may be expanded up to ten (10) evaluable subjects if at least three (3) out of five (5) subjects achieve detectable steady-state vector-derived FIX activity levels above 5%. If, after the above initial dose-level expansion, at least six (6) out of ten (10) subjects achieve detectable steady-state vector-derived FIX activity levels above 5%, then further dose level expansion of up to ten (10) additional evaluable subjects would be allowed (a total of up to twenty evaluable subjects at the starting dose level of 5 $x10^{11}$ vg/kg).

The decision to dose escalate will require the agreement of the Sponsor and the DMC.

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3.2. Study Endpoints

3.2.1. Primary Endpoints

- Clinically significant changes from baseline in the following:
  - Physical examination
  - Vital signs

- Laboratory values
- Incidence of drug-related adverse events (including inhibitor development)
- FIX incremental recovery
- Immune response against AAV capsid protein

- Laboratory parameters of thrombotic potential in any individual who reaches >150% vector-derived FIX:C activity levels after PF-06838435 infusion.

3.2.2. Secondary Endpoints

- Characterization of PF-06838435 kinetics, including:
  - Vector-derived FIX:C activity levels:
    - Peak
    - Steady-state
  - FIX antigen levels

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3.3. Study Drug Dosing

The study will consist of the following phases (See Appendix 1 Study Schematic):

- Screening period (up to 6 [±2] weeks);
- Dosing day (Day 0);
- Safety observation period (52 [±2] weeks post-infusion of PF-06838435).

The total duration of the study per subject is approximately 58 weeks (including up to 6 weeks of screening).

Subjects should be reminded to have washout of at least 96 hours (4 days) without FIX protein product or longer washout for extended half-life FIX protein product prior to any blood draw and infusion on Day 0.

Subjects will receive a bolus infusion of FIX protein product for FIX incremental recovery followed by a single intravenous infusion of PF-06838435 on Dosing day (Day 0). The complete dose of PF-06838435 will be infused via infusion pump over a period of up to 60 minutes under medical supervision.

4. General Statistical Considerations

In general, the following rules will be followed for all applicable analyses contained in this analysis plan, unless otherwise specified. Analysis populations used in specific analyses will be noted in the tables/listings.

C**ontinuous variables** will be summarized using descriptive statistics including: the number of non-missing values, mean, standard deviation, median, minimum and maximum. Means and medians will be presented to one decimal place beyond that which the data was captured. Standard deviations (SD) will be presented to two decimal places beyond that which the data was captured. Minimum and maximum will be displayed to the same number of decimal places as that which the data was captured. In case of non-normally distributed variables (such as some laboratory parameters), the geometric mean may be calculated.

C**ategorical variables** will be summarized by count and percentage. All percentages will be rounded to the nearest integer. The percentage will be suppressed when the count is zero. Unless otherwise specified, the denominator for all percentages will be the number of subjects in each treatment arm with non-missing data for a given summarization.

Baseline will be defined as the last non-missing measurement (that can be used for data analysis) taken prior to PF-06838435 infusion.

Study day, that is the start/stop date of an event, will be calculated as (date of event – first PF-06838435 infusion date) if event date is prior to PF-06838435 infusion date; Study Day will be calculated as (date of event – first PF-06838435 infusion date+1) if event date is on or after PF-06838435 infusion date.

Unscheduled visits will not be included in table summaries but will be included in the data listings.

<u>Handling of incomplete or missing data:</u>

No imputation will be applied for missing data for the analyses of safety or efficacy endpoints.

Data presentations:
Disposition and safety analyses will be presented for all subjects. All efficacy analyses will be presented overall and by regimen (prophylaxis and on-demand) as appropriate.

All analyses will be conducted using SAS version 9.2 or higher.

4.1. Sample Size

The sample size is based on the need to establish the initial safety and kinetic profile of PF-06838435. Up to 30 evaluable subjects will be evaluated in the study.

There are no formal statistical hypotheses related to the objectives of the study. Thus, the sample size is based on clinical rather than statistical considerations.

4.2. Randomization and Blinding

This is a non-randomized open-label study.

4.3. Analysis Set

4.3.1. Safety Analysis Set

The safety analysis set is defined as all subjects who receive the infusion of PF-06838435. The analysis of safety and efficacy will be performed in this population.

4.3.2. All-Enrolled Analysis Set

The all-enrolled analysis set is defined as all subjects who signed informed consent. Subject disposition will be reported in this population.

4.3.3. Pharmacokinetics (PK) Analysis Set

The PK analysis set will include subjects who have received PF-06838435 and have collected vector-derived FIX:C activity levels enabling acceptable determination of the peak and steady-state derived activity level.

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4.3.5. FIX Incremental Recovery Analysis Set

The FIX incremental recovery analysis set will include subjects who have received 100 IU/kg of FIX protein product infusion and have completed a blood sample collection

within the first 3-hours post infusion for FIX protein product enabling determination of FIX incremental recovery. The FIX incremental recovery analysis set will be used for the summary of FIX incremental recovery described in Section 10.1.

5. Subject Disposition

5.1. Disposition

Subject disposition will be summarized by dose group for all subjects in the all-enrolled analysis set. This table will present the count and percentage of subjects in each analysis set as defined in Section 4.3, number screen-failed, number completed, and number discontinued by primary reason. The duration on study (date of withdrawal or completion – date of PF-06838435 infusion + 1) will be summarized by dose group with descriptive statistics. A data listing will be provided along the disposition table.

5.2. Protocol Deviations

Protocol deviations/violations will be presented in a data listing.

5.3. Inclusion and Exclusion Criteria

Any protocol violations regarding inclusion and exclusion criteria will be presented in a listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic and other baseline characteristics (age, race, ethnicity, weight at screening and height at PF-06838435 infusion day) will be summarized by dose group using the safety analysis set. Age will be calculated as the integer part of (Date of Informed Consent – Date of Birth)/ 365.25. For sites where only year of birth is collected, age will be calculated as (Year of Informed Consent – Year of Birth). Age will be summarized both as a continuous variable and grouped by <35, ≥ 35 years of age.

A demographic and baseline characteristics data listing will also be provided.

6.2. Medical History

6.2.1. General Medical History

The significant medical and surgical history will be summarized by dose group for each body system, preferred term and presented using the safety analysis set. A subject will be counted only once if the subject reported one or more occurrences in the same body system and preferred term.

A data listing of subjects' medical and surgical history will also be provided for subjects in the safety analysis set, which will include medical condition/surgery hemophilia relatedness, start/stop date and ongoing status of the event as well.

6.2.2. Baseline Hemophilia History and Hemophilia Bleed Treatment History

Hemophilia history at screening including severity criteria, blood type, Rh factor, number of days of exposure to pd-FIX or rFIX product (<50, ≥50), inhibitor history (positive Bethesda titer, Family history of inhibitor), and allergy/anaphylaxis history (any history of Allergic type or Anaphylaxis reactions associated with administration of FIX products) will be summarized by dose group. Detailed data of each subject will be provided in data listings which will also include date of diagnosis, genotype and HLA type.

The annual bleeding rate will be reported as the total number of bleeding episodes in the 52 weeks prior to Screening Visit and will be summarized for prophylactic subjects, on-demand subjects, and overall by dose group.

For prophylactic subjects, number of prophylactic infusions in the past 12 weeks and 52 weeks prior to screening will be summarized by dose group. Number of spontaneous and traumatic bleeds in the same time periods will also be summarized by dose group. For on-demand subjects, the number of traumatic and spontaneous bleeds in the 52 weeks prior to screening will be summarized by dose group.

Prior (26 weeks preceding screening) and current FIX product, treatment regimen, dose, schedule, start and stop date will be also summarized overall, by regimen (Prophylaxis vs. On-demand), and dose group. FIX treatment information will also be presented in listings.

6.2.3. Target Joint History

Target joint (per protocol definition) history (52 weeks preceding screening) collected at screening which includes joint type and symptoms, will be summarized using data from subjects in the safety analysis set and presented by regimen (Prophylaxis vs. On-demand), dose group, and overall. Detailed data of each subject will be provided in data listings which will also include onset date and number of bleeds during the last 52 weeks.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Prior and Concomitant medications will be summarized separately by anatomical therapeutic chemical, medication names and dose group using the safety analysis set. Prior medications include all medications taken within 30 days prior to screening to the PF-06838435 infusion date.

Concomitant medications are any medication or substance that has a stop date that is on or after the date of PF-06838435 infusion.

Prior and concomitant medication will be coded using WHODRUG version June 1, 2015 (will be updated once per year).

Data on both prior and concomitant medications will be displayed in a data listing. Number of days from infusion of PF-06838435 to the start/stop date of prior or concomitant medication will be included.

Medications with start/stop dates that are partially missing will be analyzed in the summary tables as follows; Original dates will be displayed in the listings.

- If the start date is partially missing: a '01' will be used for the day and 'Jan' will be used for the month
- If the stop date is partially missing: a '28', '29', '30', or '31' will be used for the day (depends on the month and the year) and 'Dec' will be used for the month.

If the start date of a concomitant medication is completely missing, then the therapy will be included in the concomitant medications summary table if the stop date of the medication is on or after the date of PF-06838435 infusion.

An additional listing will be provided for the use of corticosteroids or alternative immunosuppressive therapy in any individual who develops hepatic transaminase elevation of 1.5-fold above baseline or successively increasing over baseline.

7.2. Study Treatments

7.2.1. Extent of Exposure

PF-06838435 infusion information will be summarized in the safety analysis set by dose group. Body mass index (<30, ≥30), duration of infusion, and total dose of PF-06838435 will be summarized. A data listing will be presented along of each subject's infusion information of PF-06838435, including infusion start and stop time.

Coagulation factor IX product administered on Day 0 and Week 52 will be summarized. Summaries will be presented for type of FIX product and FIX product dose at each time point. A listing of the FIX product dosing will also be included.

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9. Safety Analysis

All safety analyses will be conducted using the safety analysis set.

9.1. Adverse Events

An adverse event (AE) is any untoward, undesired, or unplanned medical occurrence in the form of any unfavorable and unintended sign (including clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, regardless of causal relationship, occurring in a subject participating in a clinical study. In this study, bleeding episodes are not considered AEs, but bleeding episodes that meet the criteria of serious are to be reported as serious adverse events (SAEs). Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes and Preferred Terms. MedDRA version 18.0 will be used through-out the study.

An adverse event will be regarded as treatment emergent AE (TEAE) if the start date is on or after the infusion of PF-06838435 but before subject's last visit on study (or the date of withdrawal/the date of being lost to follow-up). We will use the below algorithm to derive the start date for the determination of treatment emergence when start date is partially/completely missing and the original dates will be displayed in the listings:

- If year is missing (or completely missing) then set to the PF-06838435 infusion date
- If (year is present, and month and day are missing
    - If year = year of PF-06838435 infusion date: then set to the PF-06838435 infusion date
    - If year < year of PF-06838435 infusion date: set month and day to December 31st
    - If year > year of PF-06838435 infusion date: set month and day to January 1st
- If month and year are present and day is missing:
    - If year = year of PF-06838435 infusion date, and:
        - month = month of PF-06838435 infusion date: set day to day of SPK-9001 infusion date
        - If month < month of PF-06838435 infusion date: set day to last day of month.
        - If month > month of PF-06838435 infusion date: set day to 1st day of month
    - If year < year of PF-06838435 infusion date: set day to last day of month.

- If year > year of PF-06838435 infusion date: set day to 1st day of month.

9.1.1. Incidence of Adverse Events

All AEs, including SAEs, will be presented in data listings.

Summaries of the total number of TEAEs, the number of subjects with at least one TEAE and the incidence will be presented by dose group. The number of subjects, the number of events and the incidence will also be presented by system organ class (SOC) and preferred term (PT). At each level of summarization, a subject is counted once if the subject reported one or more events.

9.1.2. Relationship of Adverse Events to Study Drug

A summary of TEAEs by relationship to study drug will be presented by dose group in a table. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “Not Related”, “Unlikely”, “Possible”, and “Related”. In the TEAE relationship table, if a subject reported multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. TEAEs that are missing a relationship or with a relationship other than “Not Related” or “Unlikely” will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship or the actual relationship respectively. Percentages will be based on the number of subjects within each dose group in the safety analysis set.

9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented by dose group in a table. The severity that will be presented represents the most extreme severity captured on the case report form (CRF) page. The possible severities are “Mild”, “Moderate”, “Severe”, “Life-threatening” and “Death”. In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects within each dose group in the safety analysis set.

9.1.4. Toxicity Grade of Adverse Event

A summary of TEAEs by toxicity grade (per protocol APPENDIX A3: TOXICITY SCALE) will be presented by dose group in a table. If a subject reported multiple occurrences of the same TEAE, only the highest grade will be presented. Treatment-emergent AEs that are missing grade will be presented in tables as Grade 4 but will be presented in the data listing with a missing toxicity grade. Percentages will be calculated out of the number of subjects within each dose group in the safety analysis set.

9.1.5. Serious Pre-dosing Adverse Events

A serious pre-dosing adverse event is any event that meets the criteria for SAE reporting and occurs after the subject signs the ICF, but before infusion of PF-06838435. Serious pre-doing events will be presented in a data listing.

9.1.6. Serious Adverse Events

Any AE reported as resulting in death, immediate risk of death (life threatening), inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital/anomaly/birth defect will be classified as a serious adverse event (SAE). An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above. In addition, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

Serious treatment-emergent adverse events (SAEs) will be categorized and presented by dose group in a table by SOC and PT in a manner similar to that described in Section 9.1.1. Treatment-emergent SAEs with relationship to study drug will also be presented in a table. A treatment-related treatment-emergent SAE is a treatment-emergent SAE with any relation to study drug other than "Not Related" or "Unlikely". Treatment-emergent SAEs that are missing a relationship will be presented in the table as "Related" but will be presented in the data listing with a missing relationship. At each level of summarization, a subject is counted once if reporting one or more events. Percentages will be calculated out of the number of subjects within each dose group in the safety analysis set.

9.1.7. Death

All subject deaths during the study will be listed. Deaths will be identified from the AE with "Outcome" recorded as "Fatal" on the AE eCRFs.

9.2. Clinical Laboratory Evaluations

For laboratory evaluations, baseline is defined as the last non-missing evaluable assessment taken prior to PF-06838435 infusion. Post-baseline laboratory results are defined as any assessment taken after the infusion of PF-06838435.

Laboratory assessments will be performed by a certified laboratory. All summaries will be based on the units provided by the central laboratory, conversion for the local labs will be performed to make the units consistent with the central laboratory results. Summary tables will use central laboratory results. Both central and local results will be included in listings.

Additional laboratory tests other than the tests listed below will be performed to assess the safety of the immunosuppressive therapy regimen, if implemented.

Laboratory parameters of thrombotic potential in any individual who reaches >150% vector-derived FIX:C activity levels after PF-06838435 infusion will be summarized by dose group and listed in a similar way for all the below analysis.

The cases of t-cell response will be described by narrative.

9.2.1. Hematology and Chemistry

Hematology and chemistry at baseline and post baseline visits will be summarized by dose group with descriptive statistics by visit and all will be presented in a data listing. Number of subjects (n), mean, standard deviation (SD), median, minimum and maximum will be presented for all change from baseline tables.

Each subject's laboratory values will be classified according to whether the test result is "low" (i.e., below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (i.e., above the upper limit of normal [ULN]). A shift table of minimum and maximum on-study records will be created by baseline classification. Additionally, the abnormality categorical data will be summarized in this shift tables comparing the results at the end of study visit at Week 52 with those at the baseline visit.

Liver function tests (LFT) will be similarly summarized. Baseline and post baseline visits will be summarized by dose group with descriptive statistics by visit and all be presented in a data listing. Number of subjects (n), mean, SD, median, minimum and maximum will be presented for all change from baseline tables. Each subject's laboratory values will be classified according to whether the test result is "low" (i.e., below the LLN), "normal" (within the normal range), or "high" (i.e., above the ULN]. The abnormality categorical data will be summarized in shift tables comparing the results at the end of study visit at Week 52, minimum post-baseline, and maximum post-baseline with those at the baseline visit.

9.2.2. Activation of Coagulation Parameters

Activation of coagulation parameters which include activated partial thromboplastin time (aPTT), INR, TAT, and TEG and/or ROTEM (at selected time-points for FIX incremental recovery assessment) result will be presented in a data listing and the actual and change from baseline will be summarized by dose group in a table. In addition, change from baseline will be summarized for all post-baseline visits. INR, TAT, TEG, and ROTEM are only collected in subjects with > vector-derived FIX:C activity levels >150% of normal are achieved.

9.2.3. Bethesda Assay for Inhibitor Assessment

FIX Inhibitor results by Bethesda Assay from the central and local lab will be presented in a data listing.

9.2.4. Hepatitis and HIV Status

Hepatitis (HBsAg, HBcAb, HBV-DNA positivity) and HIV status as well as other serology tests, if implemented at Screening and CD4 will be summarized by dose group and presented in the same table and listing for subjects' hemophilia history.

9.2.5. Neutralizing antibody to AAV

Neutralizing antibody to AAV result from the central lab will be presented in a data listing.

9.2.6. Urinalysis

Urinalysis result from the central lab will be presented in a data listing.

9.2.7. Additional Immunology Tests

PBMCs result by IFN-γ ELISPOT to assess cellular immune responses to AAV capsid and to FIX as well as PAXgene for RNA will be presented in a data listing.

9.3. Vital Sign Measurements

For vital sign evaluations, baseline is defined as the last non-missing evaluable assessment taken prior to PF-06838435 infusion. Vital signs include systolic and diastolic blood pressure, pulse, respiratory rate, and temperature. Summary tables will be presented by dose group for vital sign data, including systolic blood pressure, diastolic blood pressure, temperature, pulse rate, and respiration rate for subjects in the safety analysis set. Changes from baseline to each scheduled post-baseline visit will be presented. All vital sign data will be presented in a listing as well. Height and weight measurements taken at screening, Day 0 pre-vector infusion and EOS will also be included in this listing.

9.4. Physical Examination

A table will tabulate physical examination results by dose group and by visit for the safety analysis set. At each visit CRF captures the status of a body system and any finding associated with the body system as normal, abnormal, or not done. The by-visit summary will include the number and percentage of subjects with each physical examination outcome for the following body systems: skin; head, eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; endocrine/metabolic; genitourinary; neurological; blood/lymphatic; musculoskeletal; and other. This categorical data will also be summarized in a shift table comparing results at each post-baseline visit with baseline by body system. Physical examination results for all subjects will be presented in a listing.

10. Pharmacokinetics

10.1. FIX Incremental Recovery

The FIX incremental recovery analysis will be using subjects in FIX incremental recovery analysis set. Blood samples for FIX activity will be collected pre-infusion of the FIX protein product and at least one sample within 3-hours post infusion. FIX activity -time

data along with the FIX antigen data will be presented in listings and summarized by dose group in a table.

Incremental recovery is determined as the peak factor level recorded within 3-hours after infusion and is reported as [IU/ml]/[IU/kg] using the following formula:

[(Activity IU/mL peak post infusion) – (Activity IU/mL pre-infusion)] / (IU/kg infused)

10.2. Vector-derived FIX:C Activity

The analysis of peak FIX:C activity will utilize summary descriptive statistics and individual subject listings and FIX Activity graphs will be presented and summarized by dose group for all vector-derived FIX:C activities by scheduled time-point.

FIX:C activity versus time will be plotted for each subject and the geometric mean concentration versus time plotted by dose group. Steady-state geometric means will be calculated for each individual and summarized for the whole group by dose group will be calculated.

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12. Interim Analysis

No formal interim analyses are planned.

13. References

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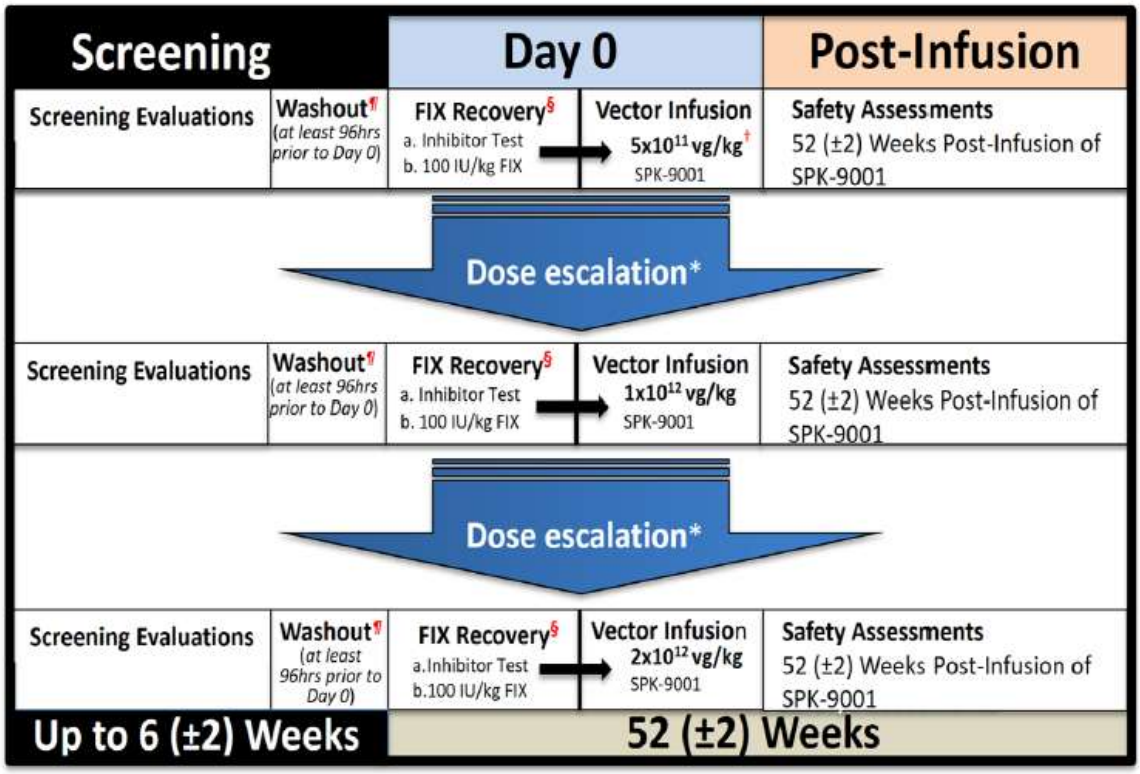
11. Appendices

Appendix 1 Study Schematic



¶ 96 hours (4 days) washout for pd- or rFIX [or up to 168 hours (7 days) washout for extended half-life rFIX]

§ FIX incremental recovery for FIX products up to 24 (±1) hours after the infusion of the FIX products.

† First two subjects at the starting dose level will be infused at least 2 weeks apart.

* Dose escalation criteria: Please see Section 3.2.2

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