Protocol C3731001

A Phase 1/2, Open-Label, Adaptive, Dose-Ranging Study to Assess the Safety and Tolerability of SB-525 (PF-07055480) (recombinant AAV2/6 human Factor 8 Gene Therapy) in Adult Subjects with Severe Hemophilia A

Statistical Analysis Plan (SAP)

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol /Amendment	Rationale	Specific Changes
1	Protocol Amendment 3 31 Jul 2018	N/A	N/A
2	Protocol Amendment 4 05 May 2020	Transfer to Pfizer template and update to reflect changes in Protocol Amendment 4	Section 2, Introduction: All references to the Safety Monitoring Committee were updated to external Data Monitoring Committee to align with the Pfizer template language. Section 2.1, Study Objectives, Endpoints, and Estimands: The endpoints language was updated to provide clarity. No changes were made to the study objectives. Section 2.2, Study Design: Duration of study was extended to 5 years from a 3-year study to ensure appropriate long-term follow-up, now including: - 2 additional study visits (Months 48 and 60) and every 6-months interim phone calls (Months 42 and 54). The Protocol ID and study intervention nomenclature were also updated to reflect both the legacy and the Pfizer references as noted below. This is a global change within the document. Protocol ID: SB-525-1603 (Pfizer reference: C3731001) Study intervention reference: SB-525 (Pfizer reference: PF-07055480) Some assessments initially done until W52 only have been added on an annual basis: Electrocardiogram, EuroQoL five dimensions, 5 levels questionnaire (EQ-5D-5L), von Willebrand Factor measurement and study drug antibodies

			neutralizing testing. Additionally, total anti-adeno-associated virus (AAV) antibodies will also be assessed. Sections 3.1.1 and 6.1.1, Incidence of Adverse Events and Serious Adverse Events: From Month 36 through to the end of study (Month 60), only the following adverse events (AEs) and the associated concomitant medications will be actively collected: Serious adverse events (SAEs); Non-serious AEs determined to be related to study intervention by the investigator or where causality is unknown. Section 3.1.2, Factor VIII Activity: The laboratory requirements for factor VIII clotting protein (FVIII) activity were updated to clarify that all samples collected from participants for FVIII activity levels will be analyzed by central and local laboratories. Clarified data handling rules and added windowing specifications for FVIII Updated time windows for geometric mean calculations for FVIII to be done by year (1, 2, 3, 4, 5) Updated from 72 hours, will now exclude from analysis any FVIII value that was assessed within 96 hours after a FVIII infusion. Section 3.2.1, AIR and Section 3.2.2, ABR: Corrected the algorithm to be used for post-infusion annualized infusion rate (AIR) and annualized bleeding rate (ABR) calculations, and specified “0” to be used if no events were recorded for an observation period. Clarified exact days to be used for yearly windowing for ABR and AIR.

			Section 3.2.2, ABR: Added “Total” (treated+untreated) ABR calculation for post-study drug infusion. Removed version of post-study drug infusion ABR which does NOT exclude any days after routine prophylaxis is resumed. Sections 3.2.3 and 6.2.3, EQ-5D-5L: Information on EQ-5D-5L Index score was added. Sections 3.2.5 and 6.2.5, Vector Shedding: For vector shedding analyses, removed ‘overall’ (across specimen types), and added the summary of time to peak value. Section 3.5.1, Adverse Events: Treatment-emergent adverse event (TEAE) definition changed to Pfizer’s standard that became effective May 2019: “An adverse event will now be considered a TEAE if the event started during the effective duration of treatment.” Section 4, Analysis Sets: The populations for analyses were revised. “Intent-To-Treat” population was removed since this population is the same as the Safety population (Safety is now considered primary). “Enrolled” analysis set was added. And “Per Protocol” was changed to “Evaluable” with modifications. Removed, “and have at least one post-baseline safety assessment” from the definition of the Safety population that is given in the protocol amendment 4. The Safety population will be all participants who received study intervention. Section 5.3.1, COVID-19 Considerations: Added analyses to assess the impact of COVID-19. Section 5.2.1.1:

			Added yearly windowing specifications for AIR, ABR, and AEs. Section 6.5.5, Hemophilia History, Medical History, and Concurrent Medical Conditions: Hemophilia History, for Time (days) since last bleeding episode, changed algorithm to make the days relative to date of study drug infusion, rather than informed consent date.
3 29 Feb 2024	Protocol Amendment 5 30 Mar 2023	Changes made for clarity, completeness, and consistency with Protocol Amendment 5 and for a more accurate summary and statistical analysis	Added endpoints and data reporting for optional liver biopsy substudy (sections 2.1, 3.3.6, and 6.3.7). Updated value used for analysis purposes when original one-stage clotting assay and chromogenic assay results are reported as <0.010 IU/mL and <0.30 IU/mL, respectively, to 0.009 IU/mL (section 3.1.2). Added clarifying text on which data (bleeds and FVIII infusions required to treat the bleeds) have to be entered in eDiary in the event a participant resumes prophylaxis after Month 24 visit (section 3.2). Removed calculation of within-participant absolute difference and percent reduction from pre-IP infusion AIR for reasons other than prophylaxis (sections 3.2.1 and 6.2.1). Added clarifying text on summary of treated and total ABR by location type and by cause (sections 3.2.2 and 6.2.2). Added time to last of 3 consecutive negative results and time to last positive result prior to 3 consecutive negative results to vector shedding summaries (sections 3.2.5 and 6.2.5). Added details on FVIII antigen imputation for results reported as BLoQ and cases in which the assessments will be excluded from summaries (section 3.3.1).

			Corrected the definition of which numerical values are considered nAb positive (3.3.2). Updated summaries related to FVIII steady state. (sections 3.3.5 and 6.3.6). Added clarifying text on which AEs are considered TEAEs (section 3.5.1) and updated AE summaries presented (section 6.6.1). Removed summary/listing of assessments not performed before, during and after the COVID 19 period (section 5.3.1). Removed plot of FVIII activity vs. number of treated bleeding episodes calculated at 4 week and/or 2 week intervals (section 6.1.2). Clarified that the summary of geometric mean of FVIII activity is applicable to Cohort 4 only (section 6.1.2.1). Added the option of performing analyses using an Evaluable population for AIR and ABR (sections 6.2.1 and 6.2.2) Added listing of post-initiation of prophylaxis treated and total ABR for participants who initiated or resumed a FVIII prophylaxis treatment during the post-infusion period (section 6.2.2). Removed shift tables from baseline to each time point of EQ-5D-5L dimensions (section 6.2.3). Removed data listing of FVIII inhibitor titer (section 6.2.4). Added summary of Von Willebrand Factor observed values and change from baseline (section 6.3.4). Removed vital signs from baseline summaries (section 6.5.1).

			Added clarifying text on collection and summarization of concomitant medications and procedures (section 6.5.4). Added analyses to assess corticosteroid treatment after IP infusion for Cohort 4 (section 6.5.4). Added summary of medical history (section 6.5.5). Added details on the eDMC meetings (section 7.1).

2. INTRODUCTION

C3731001 (Sangamo reference: SB-525-1603) is a phase 1/2, open-label, single-dose, dose-ranging study. The dose selection and number of participants studied at each dose level will be based on safety and kinetics of circulating factor VIII (FVIII) activity levels observed in previously dosed participants.

The adaptive design of this phase 1/2 study assigns participants to PF-07055480 (Sangamo reference SB-525) dose levels based on the average of FVIII activity levels in the 2 participants of a dose level/cohort. Details are provided below.

For each cohort, the first dosed participant will be followed for 6 weeks before a second participant can be dosed. After the second participant in a cohort is followed for 6 weeks, the external Data Monitoring Committee (eDMC) will meet and recommend either a dose escalation, dose de-escalation, or cohort expansion (with potential reassessment of participant's data) based on their review of the cumulative data available from the first 2 participants of a cohort.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3731001. 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.

Any deviations from the SAP will be described in the Clinical Study Report.

2.1. Study Objectives, Endpoints, and Estimands

Estimands have not been defined for this study.

Objectives	Endpoints
Primary objective	Primary endpoints
• To evaluate the safety and tolerability of SB-525 (PF-07055480).	• Incidence of adverse events (AEs) and serious adverse events (SAEs) including clinically significant changes in physical examination, clinical laboratory assessments, immune parameters, vital signs, electrocardiogram (ECG), liver imaging
• To evaluate the time-course profile of FVIII activity after dosing with SB-5-25 (PF-07055480).	• Changes in circulating FVIII activity
Secondary objectives	Secondary endpoints
• To evaluate clinical impact (efficacy and quality of life) on hemophilia after dosing with SB-525 (PF-07055480).	• Change from baseline in use of FVIII replacement therapy and frequency and severity of bleeding episodes • Change from baseline in the EuroQol, 5 dimensions, 5 levels (EQ-5D-5L)
• To evaluate immune response to FVIII.	• Measurement of FVIII inhibitor level

• To evaluate vector shedding of adeno-associated vector 2/6 (AAV 2/6).	• Detection of adeno-associated vector 2/6 (AAV2/6) vector deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) in plasma, saliva, urine, stool and semen
Exploratory objectives	Exploratory endpoints
• To evaluate the concurrence between FVIII levels by enzyme-linked immunosorbent assay (ELISA) (FVIII antigen) and by FVIII activity assays.	• Measurements of FVIII antigen levels
• To further investigate SB-525 (PF-07055480) mechanism of action and immune responses.	• Measurements of neutralizing activity and antibodies to AAV2/6, as well as T-cell responses to AAV2/6 and FVIII • Measurements of von Willebrand Factor (vWF), C-reactive protein (CRP) and interleukin-6 (IL6)
Optional liver biopsy substudy only: • To evaluate vector integration in the liver • To evaluate the histopathology of the liver tissue • To assess the expression of protein and/or RNA levels of FVIII and other biomarkers of interest in the liver	• For the integrations analyses (as feasible, ie, depending on the quantity of biological material collected): the number and location of integration sites, the location of the integration sites relative to transcription start sites, the nature of the inserted sequence, the frequency of insertions, and the frequency and distribution for each size and type of insertion • Other exploratory endpoints (as feasible): histopathology assessment (eg, presence of fibrosis assessment, presence of lymphocytic invasion), protein and/or RNA expression of FVIII and selected biomarkers (eg, Grp78, Gal3BP)

2.2. Study Design

Number of Participants:
Approximately 20 participants may be enrolled in this study. The dose selection and number of participants studied at each dose level will be based on safety and the cumulative kinetics of circulating FVIII levels observed in previously dosed participants.

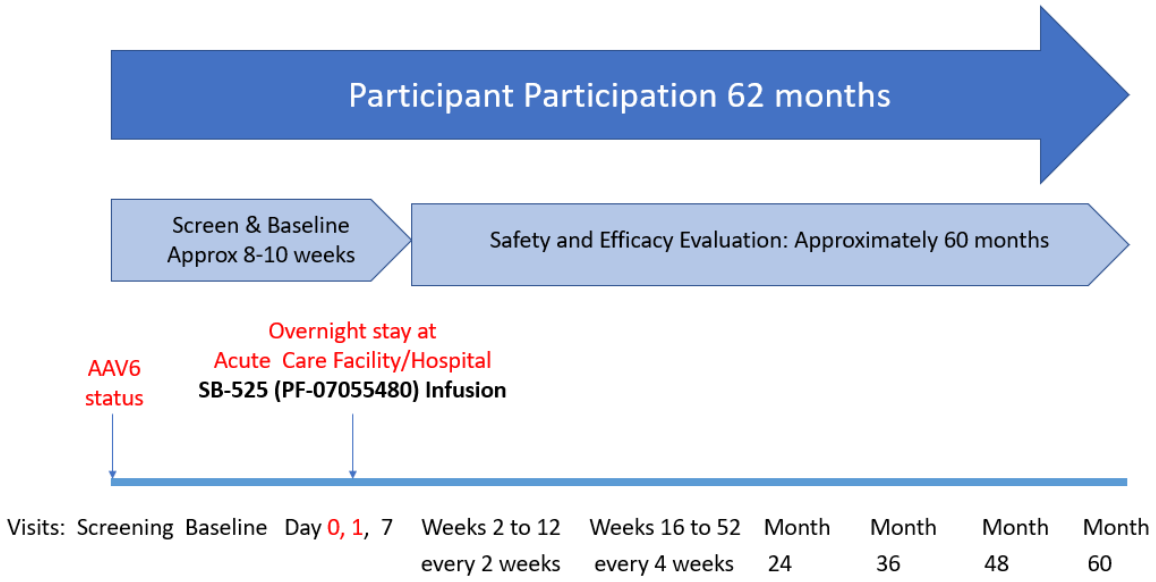
Intervention Groups and Duration:
The possible clinical dose level range will be from 6×10^{11} vector genome (vg)/kilogram (kg) to 6×10^{13} vg/kg, with a starting dose of 9×10^{11} vg/kg, which is expected to yield >5% normal FVIII levels in 57% of treated participants. Several dose levels may need to be studied to identify a safe and tolerable therapeutic range. If observed FVIII levels at the starting dose level of 9×10^{11} vg/kg are higher than anticipated, then dose de-escalation to 6×10^{11} vg/kg will be considered.

Dose levels considered include:

Possible Total Recombinant Adeno-Associated Viral Vector (rAAV) Dose (vg/kg)
6×10^{11}
9×10^{11}
1.2×10^{12}
2×10^{12}
4×10^{12}
6×10^{12}
1×10^{13}
2×10^{13}
3×10^{13}
4×10^{13}
5×10^{13}
6×10^{13}

The duration of study participation will be approximately 62 months for each participant, divided into approximately 8 weeks (2 months) for screening, and 60 months study follow-up following a single infusion on the visit, “Day 0”. Accrual is planned for 20 months.

Figure 1. C3731001 Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

This section describes the variable definitions and methods of derivation. Planned analyses and data presentations are described in Section 6.

3.1. Primary Endpoints

3.1.1. Incidence of Adverse Events and Serious Adverse Events

For Years 1 to 3, all serious and non-serious AEs will be collected. For Years 4 and 5, all SAEs (regardless of relation to study intervention) and non-serious AEs determined to be related to study intervention by the investigator or where causality is unknown will be collected.

Incidence of AEs and SAEs, include clinically significant changes from pre vector dosing in:

- physical examinations;
- clinical laboratory assessments;
- immune parameters;
- vital signs;
- ECG;
- liver imaging.

Abnormal findings that meet the criteria for AE reporting in this study are to be reported as AEs, and thus will be included in the primary endpoint summary table.

3.1.2. Factor VIII Activity

All samples collected from participants for plasma factor FVIII activity levels will be analyzed by central and local laboratories. In the central laboratory, FVIII activity will be assessed both by chromogenic and one-stage clotting assays. In local laboratories, FVIII activity will be assessed by chromogenic or one-stage clotting assay based on local laboratory's usual practice. Only central laboratory results will be used for analysis. Raw values reported as below the limit of quantification (BLoQ) will be converted to a numeric value for analyses (summaries and plots). The numeric value of 0.009 international units (IU)/ milliliter (mL), or 0.9 % normal, will be assigned prior to analysis for both one-stage clotting assay and chromogenic assay when the originally reported results were <0.010 IU/mL and <0.030 IU/mL, respectively. Summary tables and plots will use "% normal" as units, where % normal = IU/ mL x 100.

FVIII activity assessments assigned to a protocol-defined visit, will be analyzed for that visit. If FVIII activity is assessed as an unscheduled visit, the assessment date will be converted to a day relative to the investigational product (IP) infusion and divided by 7. The integer value of the quotient will be the 'week' assigned to the unscheduled assessment. If the derived week for an unscheduled assessment falls within the visit window of a protocol-defined visit, the unscheduled assessment result will be included in summaries and analyses for the mapped protocol-defined visit. Additional windowing details for mapping weeks to visits can be found in the Analysis and Reporting plan.

Per protocol, if a participant has FVIII replacement therapy around the day of a visit when FVIII activity measurement is scheduled, sample collection should be postponed at least 48 or 72 hours based on the FVIII product used (standard half-life or extended half-life respectively). For all FVIII activity summaries and analyses (including plots), any FVIII activity values measured within 96 hours after administering exogenous FVIII replacement therapy will be excluded as ineligible. In addition, FVIII activity assessments collected after a participant initiates or resumes a prophylaxis regimen will be excluded. If there are multiple observations for an individual in the same time window, for all FVIII activity analyses with the exception of geometric mean analyses, the average of an individual's FVIII activity values within the same time window will be used.

A listing of individual FVIII activity values for each participant will show assay used, observed values in collected units and in % normal units, visit name (including unscheduled visits), and the analysis visit (the visit to which the value has been slotted, either from the visit name, or derived by taking the integer part of relative day/7). Measurements within 96 hours after a FVIII replacement infusion or after a participant initiates or resumes a prophylaxis regimen, will be flagged in the listing and excluded from plots.

Group-level plots will be limited to protocol-defined study visits. If the derived week for an unscheduled assessment falls within the visit window of a protocol-defined visit, the unscheduled value will be displayed. Individual-level plots will use unslotted unscheduled

visit data points. Baseline for FVIII activity is defined as the latest valid measurement prior to IP infusion.

3.1.2.1. Factor VIII Activity Geometric Mean

The primary endpoint of time course profile of FVIII activity will be determined for the participants in the cohort administered the dose level intended for Phase 3 (ie, Cohort 4, 3×10^{13} vg/kg). The geometric mean for each participant will be calculated and summarized with descriptive statistics across the cohort for each assay type, for each year of the study. The geometric mean is the antilog of the mean of the log-transformed values.

FVIII activity over time will be calculated for each participant as the geometric mean of all eligible FVIII activity measurements within each yearly window. The summary statistics across participants in each cohort, for each observation period, will include sample size, arithmetic mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. Calculation of the geometric mean for Year 1 will use all available data points beginning with the week considered to be when 'steady state' (see Section 3.3.5 for more detail) has been achieved (eg, Week 9), through Week 52 (Weeks up to 53 will be included per the Schedule of Activities [SoA]), including those measured at unscheduled visits, and those where multiple observations may fall into the same time window. If multiple eligible FVIII activity observations are collected on the same day, the average level of these observations will be used for the given day. FVIII activity measurements within 96 hours after a FVIII replacement infusion, as well as those collected after routine prophylaxis has been initiated or resumed, will be excluded.

The geometric mean of FVIII activity will be similarly calculated for each assay type in the following designated yearly time periods (allowing for the 1 month flexibility in the SoA visit schedule after the first year) as indicated below:

Time period	Geometric Mean Window
Week 54 through Week 108 (Week 104±4 weeks)	FVIII Activity Year 2
Week 109 through Week 160 (Week 156±4 weeks)	FVIII Activity Year 3
Week 161 through Week 212 (Week 208±4 weeks)	FVIII Activity Year 4
Week 213 through End of Study (Week 260±4 weeks)	FVIII Activity Year 5

If a participant has not yet been followed for the full interval or has missing data, then all available data will be included to calculate geometric mean despite the missed measurements.

3.2. Secondary Endpoints

An e-Diary on a handheld device is to be provided to each participant at baseline, which is to be used until the end of study. The participants are required to enter any occurrence of bleeding episodes (including date, time, location, and etiology) and any exogenous FVIII replacement (including date, time, reason, and dose) required to treat the bleeds in the e-Diary throughout follow-up regardless of whether or not the participant has initiated or resumed prophylactic therapy. If a participant has to initiate or resume FVIII prophylaxis

treatment, prophylaxis FVIII infusion data will not have to be reported on the e-Diary after Month 24 but the prescribed FVIII replacement regimen will be recorded in the eCRF by the sites and used to derive infusion data. On-demand and preventative infusions will continue to be required to be reported on the e-Diary throughout follow-up.

The protocol recommends prophylaxis FVIII treatment for up to approximately 2 weeks post PF-07055480 infusion (and may be used longer than 2 weeks, per investigator discretion), to provide protection against bleeding while allowing sufficient time for PF-07055480 to start FVIII expression. Participants are then switched to on-demand regimen. The first 3 weeks following treatment with PF-07055480 will not be considered in the analysis of annualized infusion rate (AIR) and annualized bleeding rate (ABR), to exclude contributions from prior routine prophylaxis, which could have been continued during this period.

3.2.1. Annualized Infusion Rate

The FVIII Administration electronic case report form (eCRF) and e-Diary will be used to collect each participant's pre-IP infusion FVIII medication details (including reason for infusion) beginning 30 days prior to the Screening visit through the Baseline visit (eCRF), and from Baseline to just before the IP infusion (e-Diary).

For pre-IP infusion, the AIR will be calculated in two ways:

- [(number of FVIII replacement infusions <u>for reasons other than prophylaxis</u> prior to IP infusion)/([date of IP infusion – date of screening] + 30)]*365.25.
- [(number of FVIII replacement infusions <u>for any reason</u> prior to IP infusion)/([date of IP infusion – date of screening] + 30)]*365.25.

Reasons for FVIII replacement therapy other than prophylaxis will include selective prevention of bleeding, prophylaxis for invasive procedures, and bleeding. In case a frequency other than "Once" is selected, the number of FVIII infusions to be added to the numerator of the above will be calculated based on the frequency of FVIII infusions and duration of treatment. A frequency of once per day will be used for frequencies listed as burst, taper, and titrate.

For post-IP infusion, the annualized infusion rate will be assessed as [number of FVIII replacement infusions starting at 3 weeks (ie, Day 22 post-IP infusion) after IP infusion]/(number of days in the observation period for the participant in years). If the participant discontinued from study before the end of the prespecified time period, the last date in the observation period will be the date of study discontinuation. For all participants, post-IP infusions (and days for the denominator) will be counted beginning on Day 22, and will stop counting when (the first of) any of the following things happen:

1. The subject completes or discontinues (this day will be counted if data were collected).
2. Data cut or freeze date (this day will be counted if data were collected).

The number of days in the observation period will be calculated as (date of data cut [or conclusion date] – [date of IP infusion + 21 days] + 1), which will then be annualized within the AIR formula. All infusions during the observation time period for any purpose (to treat bleeding, for preventive purpose, perioperative, or if FVIII prophylaxis regimen is initiated or resumed) will be included in the calculation of AIR. If no FVIII replacement infusions are reported during an observation period, AIR will be reported as zero.

A within-participant absolute difference, as well as percent reduction from pre-IP infusion AIR, will be calculated and summarized for the pre-study infusion calculation method that includes FVIII replacement therapy for any reason.

The five yearly windows defined in Section 5.2 will be used for this AIR analysis. An additional observation period is defined for the entire length of follow-up, >week 3 through Year 5.

3.2.2. Annualized Bleeding Rate

The number of bleeding episodes (BEs) during 12 months prior to the Screening visit will be collected in the Hemophilia History eCRF directly and will be used as the pre-screening rate. This form does not distinguish between treated or untreated bleeding episodes, only "total" pre-screening rate will be available.

The post-IP treated ABR will be calculated as:

[(number of BEs requiring FVIII treatment recorded for the participant starting 3 weeks after IP infusion)/(number of days in observation period for the participant)]*365.25.

If a FVIII prophylaxis regimen is initiated or resumed for a participant, then the time period (beginning with the first day of prophylaxis initiation or resumption) will be excluded from the treated ABR. The bleeding events after prophylaxis initiation or resumption will be excluded and the time period while on prophylaxis regimen will be deducted from the observation period, as well.

For all participants, treated bleeds (and days for the denominator) will be counted beginning on Day 22, and will stop counting when (the first of) any of the following happen:

1. The subject initiates or resumes routine prophylaxis (first day of resumption will not be counted);

2. The subject completes or discontinues (this day will be counted if data were collected);

3. Data cut or freeze date (this day will be counted if data were collected).

The number of days in the observation period will be calculated as (date of day before start of prophylactic dosing [or date of data cut or conclusion date] – [date of IP infusion + 21 days] +1) which will then be annualized within the treated ABR formula. If no treated

bleeding episodes are reported during an observation period, treated ABR will be reported as zero.

During the post-IP period, multiple concurrent BEs (eg, two or more BEs that occur on the same date and time but in different sites in a participant) will be recorded as one bleed for overall treated ABR, but as separate BEs for that participant for treated ABR by location type (one episode for each unique location type, if they are different). Both spontaneous and traumatic treated bleeds will be counted towards the derivation of overall treated bleeding rate. BEs associated with a surgical procedure (perioperative and/or during the surgical rehabilitation period) will not be included in the treated ABR calculation.

Because only total ABR is available for pre-screening, overall total post-IP ABR will also be calculated, including BEs with and without FVIII treatment. A within-participant absolute difference, as well as percent reduction from pre-screening ABR, will be calculated for total ABR and summarized.

Treated and total ABRs will also be derived by location type (joint, target joint, soft tissue/muscle/other), by cause (spontaneous BE and traumatic BE), and by BE severity (mild, moderate, severe).

The five yearly windows defined in Section 5.2 will be used for treated and total ABR analysis. An additional observation period is defined for the entire length of follow-up, >week 3 through Year 5.

3.2.3. EQ-5D-5L

Developed by the EuroQoL Group, the EQ-5D-5L (EuroQoL, 5 dimensions, 5 levels) is considered the premier measure of health status used in the assessment of the Quality Adjusted Life Year. It measures 5 dimensions of health on a 5-point scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Also included is a visual analog scale (VAS) anchored by worst and best imaginable health on a 0 to 100 scale where participants are asked to indicate where on the scale they rate their current health.

Missing data will not be imputed, which means missing individual question responses will lead to missing dimension scores and Index (total) score. EQ-5D-5L baseline is the latest evaluation prior to PF-07055480 infusion.

Each of the 5 dimensions (ie, ‘Mobility’, ‘Self-care’, ‘Usual activities’, ‘Pain/discomfort’, and ‘Anxiety/depression’) in the EQ-5D-5L questionnaire is assessed with 5 levels of perceived problems:

Level	Description	Score
Level 1	No problem	1
Level 2	Slight problems	2
Level 3	Moderate problems	3

Level 4	Severe problems	4
Level 5	Extreme problems	5

A health state is defined by the combination of one level from each of the 5 dimensions. There is a total of 3125 possible health states. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problem with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

The Index score (total score) of EQ-5D-5L will be obtained, according to the health state defined by the 5 dimension scores, from the Crosswalk Index value calculator and table lookup document under the target country population. For the clinical study report, weights under the US population will be used to obtain the Index score.

3.2.4. FVIII Inhibitor

FVIII inhibitor assessments will be collected according to protocol-specified SoA. Results provided by the central laboratory as <0.6 Bethesda units (BU) will be considered as negative.

3.2.5. Vector Shedding

Samples of plasma, saliva, urine, stool, and semen will be collected as specified in the protocol SoA for analysis of vector shedding. Peak values, time to peak value, time to undetectable/negative vector (defined as time to first of 3 consecutive specimens under the limit of detection), time to last of 3 consecutive negative results, and time to last positive result prior to 3 consecutive negative results will be derived for each specimen type. A result indicating it is below the lower limit of quantification will be shown in the listing as reported and will be set as 1 for plotting purposes.

3.3. Exploratory Endpoints

3.3.1. FVIII Antigen

Blood samples will be collected as specified in the SoA of the protocol and as specified in the Laboratory Manual to measure FVIII antigen levels. Results reported as BLoQ will be set as 0.009 IU/mL (0.9%) for analysis purposes. Any sample taken within 96 hours after administering exogenous FVIII replacement therapy will be excluded from summaries and analysis. In addition, FVIII antigen data collected after a participant initiates or resumes a prophylaxis regimen will be excluded.

3.3.2. Immunogenicity

The following immunogenicity assessments (listed in the table of protocol-required safety laboratory assessments) will be performed over time and reported:

- Total and neutralizing antibodies to AAV2/6 (anti-drug antibodies [ADA] and neutralizing antibodies [nAb]):

- For nAb (test MRD10), numerical values ≥ 0.34 will be considered as 'negative' and numerical values <0.34 will be considered as 'positive'.

- Cellular responses against FVIII and AAV (ELISPOT assay);

- Measurements of C-reactive protein (CRP) and interleukin-6 (IL-6).

3.3.3. Von Willebrand Factor

Blood samples will be collected, prepared, and stored as specified in the SoA of the protocol and in the Laboratory Manual.

3.3.4. GAL3BP and sEGFR

Expression of both soluble epidermal growth factor receptor (sEGFR) and galectin-3-binding protein (Gal3BP) will be measured at baseline in serum samples.

3.3.5. FVIII Steady State

Due to the small sample size and high inter-subject variability of PF-07055480 transgene expression, including FVIII activity levels, both mean and median values of FVIII levels using chromogenic and one-stage assays will be presented for each visit to assist in determining the onset of steady state of transgene expression.

3.3.6. Optional Liver Biopsy Substudy

An optional liver biopsy can be performed (in participants who consent to do so and as per investigator's judgement) during the post-infusion period until year 5, ie, the end of the study. The procedure may be repeated once, later in the study, to assess evolution over time (in participants who consent to do so and as per investigator's judgement).

This substudy may be proposed to any participant, unless there is a condition that, in the opinion of the investigator or a hepatologist or radiologist, would make liver biopsy contraindicated.

The exploratory objectives of the substudy are to evaluate vector integration in the liver, the histopathology of the liver tissue and to assess the expression of protein and/or RNA levels of FVIII and other biomarkers of interest in the liver (depending on collected material). A biopsy will be made upon investigator's decision; it can be performed at any time post-infusion to assess liver health, integration and FVIII in the liver, but could also be triggered by sustained elevated FVIII activity levels, by a significant FVIII activity decline, by a sustained ALT elevation > ULN or to assess the long-term gene therapy effects on the liver.

3.4. Baseline Variables

Demographics, medical history, and hemophilia history will be collected at screening visit.

Baseline variables include age, race, ethnicity, sex, weight, height, body mass index (BMI), and 12-lead ECG. Age (years) at informed consent 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 from dosing study – year of birth). Age will be summarized as a continuous variable. BMI will be calculated as [(weight in kg)/(height in centimeters [cm])^2]*10000.

3.5. Safety Endpoints

3.5.1. Adverse Events

All adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) in place at the time of data cut or data base release. AE severity will be captured using common terminology criteria for adverse events (CTCAE; version 4.03) grading. An AE will be considered a treatment-emergent adverse event (TEAE) if the event started during or after PF-07055480 infusion, or on the day of PF-07055480 infusion if the time of the AE was not collected. AEs will be assessed throughout the study as described in the SoA, and at the early termination visit, if applicable.

In addition to reporting AEs across the entire study, the five yearly windows defined in Section 5.2 will be used for AE reporting.

3.5.2. Laboratory Data

The safety and efficacy laboratory tests to be performed are provided in Protocol Appendix 2. Baseline will be defined as the last pre-infusion measurement.

3.5.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure (SBP and DBP), heart rate, respiratory rate, and temperature and will be measured during the complete physical examination. Additional measurements will occur on “Day 0” visit and “Day 1” visit. On the infusion day (“Day 0” visit) and the “Day 1” visit, vital signs will be obtained prior to infusion and then within 5 minutes of the start of the infusion, every 15 (±5) minutes for the length of the infusion, every 15 (±5) minutes until stable (±10 millimeters of mercury [mmHg]), then every 30 (±5) minutes until 2 hours post-infusions, then every 4 hours (±10 minutes) until discharge.

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

3.5.4. Electrocardiogram

Standard 12-lead ECGs will be performed according to SoA.

3.5.5. Physical Exam

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (cm) will be collected at screening only, and weight (kg) will be collected at screening and baseline only.

3.5.6. Other Safety Parameters

Chest X-ray, liver elastography, liver magnetic resonance imaging (MRI) and abdominal examination will be performed according to protocol.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Population	Description
Enrolled	All participants who sign the informed consent form (ICF) and meet all inclusion/exclusion criteria.
Safety	All participants enrolled in this study who receive any portion of study intervention.
Evaluable	All participants enrolled in the study who receive study intervention and have no significant interruptions of efficacy measurements.

5. GENERAL METHODOLOGY AND CONVENTIONS

All statistical analyses will be performed using SAS system version 9.4 or higher.

All summary statistics will be reported stratifying by cohort/dose level (planned or received, depending on the study population) and overall. Relative day 1 is defined as the date of visit "Day 0", the start of the IP infusion.

5.1. Hypotheses and Decision Rules

No formal statistical inference is planned. The analyses will be purely descriptive.

5.2. General Methods

5.2.1. Windowing

Windows may be developed for specific data points for analysis.

5.2.1.1. Yearly Windowing

The following windowing option may be used when each yearly observation period used for analysis will be 365 days. Any dates beyond 1460 days will also be included with Year 5 for analysis. Post-infusion AIR and ABR yearly windowing begins with 3 weeks after the IP infusion where day is calculated relative to the IP infusion date. Post-infusion AE yearly windowing begins on the IP infusion date.

Window name	Derivation
Year 1	Day 22 ≤ Year 1 ≤ Day 365
Year 2	Day 365 < Year 2 ≤ Day 730
Year 3	Day 730 < Year 3 ≤ Day 1095
Year 4	Day 1095 < Year 4 ≤ Day 1460
Year 5	Day 1460 < Year 5

Further details of windowing will be described separately for each endpoint in Section 2.1, as applicable.

5.2.2. Analyses for Binary Endpoints

Descriptive statistics of binary data will include the number of non-missing observations, the frequency of the observed endpoint as well as the observed proportion.

5.2.3. Analyses for Continuous Endpoints

Summary descriptive statistics for continuous variables will include the number of observations with non-missing values, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum values.

5.2.4. Analyses for Categorical Endpoints

Summary tables for categorical variables will include the number and percentage of observations for each category. Unless otherwise specified, the number of observations with non-missing values will be the denominator for percentage calculation.

5.3. Methods to Manage Missing Data

In general, missing data will not be imputed in this study, unless specified in Section 3, where individual endpoints are discussed.

5.3.1. COVID-19 Considerations

In order to assess the effect of COVID-19, the following information will be additionally listed or summarized separately for the study:

- AE associated with COVID-19.
- Protocol Deviations related to COVID-19 (important and non-important ones).

Additional COVID-related data presentations or analyses may be provided, as appropriate.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoints

6.1.1. Incidence of Adverse Events and Serious Adverse Events

During Years 1, 2, and 3 all AEs are to be collected, and during Years 4 and 5, treatment-related AEs (plus all-causality SAEs) are to be collected.

Incidence of adverse events will be presented descriptively. In addition, incidence of treatment-related adverse events will be similarly presented. Summaries will be presented by dose level and overall. AE tables by year will show columns for each dose level and overall, and separate pages for each of the five yearly periods as described in Section 5.2 (Year 1, 2, 3, 4, and 5), with denominator (number of participants still being followed at the beginning of each year) and counts (%) of participants in each, corresponding to the onset date of AE.

The incidence and severity of AEs will be tabulated and grouped by system organ class (SOC) and preferred term (PT). In addition, all serious AEs (regardless of causality) will be summarized separately. A summary table including severity graded by CTCAE version 4.03, for those events that are possible to rate, will also be provided.

6.1.2. FVIII Activity

Summary tables for central laboratory FVIII activity values, with descriptive statistics by study visit and dose level will be created. The FVIII activity values assessed by the two assays (chromogenic and one-stage clotting) will be summarized separately. Listings will be presented separately for local and central laboratory individual values, as described in Section 3.1.2.

Individual plots of FVIII activity will be created using the Safety population, with collection time in weeks post-infusion on the x-axis (including unscheduled visits), and FVIII activity on the y-axis. Separate figures will be created for one-stage clotting and chromogenic results; each figure will contain all participants from a cohort on the same graph. The plots will be created using both the original scale and the log scale.

A scatter plot of chromogenic assay versus one-stage assay results will be generated to investigate the correlation between the two assays. Measurements from all time points will be placed on the same graph, and thus a participant will contribute multiple times to the figure. Data points will be differentiated by different colors for cohorts and symbols for participants.

All FVIII analyses will be performed using the Safety analysis set. Additional analyses may be performed using an Evaluable population, if appropriate.

6.1.2.1. FVIII Activity Geometric Mean

The geometric mean of FVIII activity between the week determined to be the start of steady state (Week 9), and Week 52 (Year 1) will be summarized for Cohort 4 (3×10^{13} vg/kg) by type of assay (chromogenic and one-stage). The geometric mean of FVIII activity will also be summarized for each additional yearly interval as specified in Section 3.1.2.1.

6.2. Secondary Endpoints

6.2.1. Annualized Infusion Rate

Both pre- (for any reason and reasons other than prophylaxis) and post-IP infusion annualized rates will be summarized together, along with the difference and percent reduction with respect to the pre-IP infusion AIR (for any reason), using the Safety population by dose level. All participants, regardless of prior prophylaxis treatment status, will be included. AIR will be summarized by the time intervals as specified in Section 3.2.1.

Additional analyses may be performed using an Evaluable population, if appropriate.

Listings of FVIII replacement therapy and the annualized rates will be provided.

6.2.2. Annualized Bleeding Rate

Both pre-screening and post-IP infusion total ABRs will be summarized together with the difference and percent reduction, along with the summary of post-IP infusion treated ABR, for the Safety population by dose level. The number and percentage of participants with no bleeds post-IP infusion will also be summarized by dose level. All participants, regardless of prior prophylaxis treatment status, will be included. Post-IP infusion treated and total ABR will be summarized by the time intervals as specified in Section 3.2.2.

Separate summaries of treated and total post-IP infusion ABR by location type (joint, target joint, soft tissue/muscle/other), by cause (spontaneous and traumatic BEs), and by BE severity will be created for the Safety population stratifying by dose level.

Additional analyses may be performed using an Evaluable population, if appropriate.

Listings of BEs recorded during the study and the annualized rates will be created. The listing will additionally include treated and total post-initiation or post-resumption of prophylaxis ABR for the participants who initiated or resumed a FVIII prophylaxis treatment during the post-infusion period.

6.2.3. EQ-5D-5L

EQ-5D-5L VAS score and Index score results and change from baseline will be summarized as continuous variables by visit, stratifying by dose level (cohort) and overall (across dose levels).

For EQ-5D-5L dimensions, summary will be provided with counts and percentages of scores in each dimension by visit.

Listings of EQ-5D-5L dimension scores, VAS score, and Index score data will be created.

6.2.4. FVIII Inhibitor

The number and percentage of participants with negative results at each visit will be presented.

6.2.5. Vector Shedding

The peak value, time to peak value, and time to undetectable/negative vector (first of 3 consecutive negative results), time to last of 3 consecutive negative results, and time to last positive result prior to 3 consecutive negative results will be summarized by specimen type, stratified by dose level. Number and percentage of participants who achieved 3 consecutive negative results will be reported for each specimen. Peak value information and time to undetectable/negative vector will also be presented in a data listing. Vector genome values for each study visit will be listed by specimen type. Individual profile plots of vector genome values over time (log scale) will be presented by dose level for each specimen type.

6.3. Exploratory Endpoints

All summaries and listings of exploratory endpoints will be based on the Safety population.

6.3.1. FVIII Antigen

FVIII antigen levels will be summarized by visit and dose level and presented in a data listing.

6.3.2. Immunogenicity

The results of the following parameters will be presented in a data listing. Individual profile plots of the values over time will be presented by dose level, if appropriate.

- Total and neutralizing antibodies to AAV2/6;
- Cellular responses against FVIII and AAV2/6 (ELISPOT assay);
- Measurements of CRP and IL6.

6.3.3. Von Willebrand Factor

Von Willebrand Factor will be summarized for observed values and change from baseline by visit and dose level and presented in a data listing.

6.3.4. GAL3BP and sEGFR

Baseline values for sEGFR and Gal3BP will be presented in a data listing.

6.3.5. FVIII Steady State

Mean and median values of FVIII levels using chromogenic and one-stage assays will be presented as a box and whisker plot by visit for Cohort 4 (3×10^{13} vg/kg) to assist in determining the onset of steady state of transgene expression.

6.3.6. Optional Liver Biopsy Substudy

Liver biopsy will be performed on few participants only and most probably at different timepoints for each participant, so mainly a description of the findings for each biopsy will be provided.

6.4. Subset Analyses

Not applicable.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

All baseline characteristics will be summarized by dose level and overall for the Safety population. The following parameters will be summarized:

- Age (in years) at informed consent (IC), calculated as the integer part of (Date of IC – Date of Birth)/365.25; if only year of birth is collected, then age will be calculated as (Year of IC – Year of Birth);
- Race;

- Ethnicity;
- Sex;
- Weight (kg) at screening and baseline;
- Height (cm) at screening;
- BMI (kg/meter [m]^2) at screening (calculated as [(weight in kg)/(height in cm)^2]*10000);
- 12-lead ECG at screening, n (%) of normal result.

Listings of baseline characteristics will also be created.

6.5.2. Study Conduct and Participant Disposition

The number of screened participants will be summarized. For screen failures, the reason for screen failure will be summarized using counts and percentages. No stratification by dose level will be implemented for this analysis. Enrolled participants are those who have been screened, are not considered to be a screen failure, and who have been approved by the Medical Monitor. A participant will be considered to have completed the study if he has completed all phases of the study including the End-of-Study visit (Month 60).

The number of participants enrolled, completing the study, discontinuing from the study and the primary reason for discontinuation, and the number of deaths (if any), will be summarized (number and percentage of enrolled participants in each population used for analysis), stratifying by dose level and overall. The number of ongoing participants will be included for outputs provided prior to the final analysis.

Listings will be provided for participant disposition, along with reasons for exclusion or discontinuation. An additional participant-level listing will be provided, indicating each observation period (Year) that he entered, and his duration in that period, along with his total study duration, as of the date of data cut (or conclusion date).

Potentially important protocol deviations (corresponding to those reported as ‘Major’) will be presented in a data listing.

6.5.3. Study Treatment Exposure

The total amount of IP taken by participant (vg) will be summarized for the Safety population by dose level. The number and percent of participants receiving the intended dose and experiencing interruptions during dosing will also be summarized. The doses corresponding to the 4 cohorts are: 9x10^11vg/kg (cohort 1), 2x10^12vg/kg (cohort 2), 1x10^13vg/kg (cohort 3), and 3x10^13vg/kg (cohort 4).

A listing of IP administration will be created.

6.5.4. Concomitant Medications and Nondrug Treatments

During the first 3 years, all concomitant medications are to be recorded on the participant's eCRF, as well as any AEs related to administration of these medications.

During Years 4 and 5 post-IP infusion, only concomitant medications associated with SAEs or AEs assessed as related to investigational product by the investigator or where causality is unknown are to be recorded.

All concomitant procedures will be recorded in the eCRF throughout the entire duration of the study.

Medications will be coded with World Health Organization Drug Dictionary (WHO DD) using the most recent version in place at the time of data cut or data base release, providing Anatomical Therapeutic Chemical (ATC) level 2 and ATC level 4 codes for each medication. A medication will be considered prior if its end date is before the IP infusion, and concomitant otherwise. The number and percentage of participants taking prior and concomitant medications will be summarized by ATC codes for the Safety population. All summaries will be presented by dose level and overall. Prior FVIII replacement therapy will be defined and summarized similarly to prior medications. In a similar manner, concomitant procedures will be summarized by SOC and PT.

Prior and concomitant medications, post-IP infusion FVIII replacement therapy, previous FVIII replacement therapy, and concomitant procedures will be presented in separate listings.

To assess corticosteroid treatment after PF-07055480 infusion, the following data will be summarized and presented in a listing for Cohort 4 (3×10^{13} vg/kg):

- Duration of corticosteroid courses. All consecutive corticosteroid treatment records with ≤ 3 days between the last day of the prior record and the first day of the following record will be considered one course.

- Total duration of corticosteroid treatment per participant, defined as the sum of the duration of all courses for each participant.

Individual profile plots containing liver function data, FVIII activity, and corticosteroid use over time will be presented for Cohort 4 (3×10^{13} vg/kg).

Additionally, a listing of the participants who took steroids during the study in the Safety population will be provided.

6.5.5. Hemophilia History, Medical History and Concurrent Medical Conditions

Medical history will be summarized with counts and percentages of participants by SOC and PT for each dose level and overall for the Safety population.

Concurrent and prior conditions will be listed. A condition will be considered prior if its end date is before the IP infusion, and concurrent if its end date is after the IP infusion. In case of

missing end date, a condition will be considered concurrent if it was ongoing at screening, and prior otherwise.

Hemophilia history data will be summarized by dose level and overall for the Safety population. The following parameters will be included in the summary: time since hemophilia diagnosis (calculated as (date of IC - date of diagnosis)/365.25), hemophilia severity grade at screening, type of FVIII treatment, history of FVIII inhibitors, number of bleeding episodes in the last 12 months (overall and by severity), time since last BE (in days; calculated as date of IC - date of last BE), number of participants with target joints, and target joint/body area. A disease history listing will also be created.

At the Screening visit, the FVIII Regimen History eCRF is used to collect, "all prior FVIII treatments the subject took, starting 12 months prior to screening and ending 30 days prior to screening". This infusion data will be summarized separately as part of Prior and Concomitant Medications.

6.6. Safety Summaries and Analyses

All safety analyses, including analyses of AEs, clinical laboratory results, vital signs, ECG, and physical examinations will be conducted on the Safety analysis population.

6.6.1. Adverse Events

All AEs will be summarized for the Safety population, by dose level and overall across dose groups. AEs by Year 1, 2, 3, 4, and 5 will be presented.

Both all-causality AEs and treatment-related AEs will have similar summaries presented descriptively. All data will be included in the summary as appropriate, with clarifying footnotes describing the types of AEs collected in each reporting period.

The number and percentage of participants with any TEAE, any treatment-emergent SAE, any treatment-related TEAE, any serious treatment-related TEAE, and any TEAE leading to discontinuation from the studywill be presented for all participants by dose level and overall.

All TEAEs, treatment-emergent SAEs, and treatment-related TEAEs will be summarized by SOC and PT; all TEAEs and treatment-related TEAEs will also be summarized by SOC, PT and Common Terminology Criteria for Adverse Events (CTCAE; version 4.03) severity grade. Summaries will include the number and percentage of participants in each SOC, PT, or CTCAE severity grade by dose level and overall. Adverse events of special interest (AESI) will be identified in summaries by SOC and PT.

Separate listings of TEAEs, SAEs, TEAEs leading to discontinuation from the study, and AEs leading to death (if any) will be produced. A listing of deaths will be provided as well, including the date and information about the primary reason for death.

6.6.2. Laboratory Data

All samples will be analyzed by a central laboratory (liver panels may also be done locally in certain circumstances, only listings will be provided for local liver panel data). Likewise,

although FVIII activity assessments are to be analyzed by both local and central laboratories, only central laboratory values will be summarized, and local laboratory values will be reported in a listing. No local laboratory data will be summarized in this study.

Descriptive statistics of actual values and change from baseline for all liver function tests (LFT) will be presented by time point. Summaries will be performed based on the Safety population, by dose level and overall. All LFTs will also be presented in listings. Individual profile plots of the liver test values over time will be presented for each participant by LFT.

Safety laboratory tests and other laboratory tests specified in Section 3.5.2 will be summarized.

Laboratory values outside of a laboratory's normal ranges will be flagged as H (high, above normal) or L (low, below normal) in laboratory data listings.

Tabulations for low, normal, and high test results will be presented by visit for selected parameters. A shift table of minimum and maximum on-study records will be created by baseline classification.

6.6.3. Vital Signs

A summary table of the maximum change from baseline (increase and decrease) through Day 1 and change from baseline on Day 7 will be provided for SBP and DBP, heart rate, respiratory rate, and body temperature for the Safety population. Listings for each, and weight, will be provided based on the Safety population for each visit.

6.6.4. Electrocardiograms

A data listing will be created for ECG.

6.6.5. Physical Examination

A data listing will be created for physical examination measurements.

6.6.6. Other Safety Parameters

A data listing will be created for abdominal examination for hepatomegaly.

Data listings will also be provided for chest X-ray and liver elastography performed at screening, and all liver MRI scans. All listings will be provided using the Safety population.

7. INTERIM ANALYSES

7.1. Introduction

An interim analysis (IA) of safety and efficacy data will be conducted at one year after the last enrolled participant receives SB-525 (PF-07055480) infusion. As this is an open-label 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 pharmacokinetic/pharmacodynamic modeling, and/or to support clinical development.

Additionally, an interim analysis of safety and efficacy data may be conducted to support interactions with the national or local health authorities related to the submission and/or registration of SB-525 (PF-07055480) for use in hemophilia A patients.

This study will use an external Data Monitoring Committee (eDMC). The eDMC is independent of the study team and includes only external members. The eDMC will convene approximately every 6 months until study completion to monitor the safety and efficacy of the participants. Ad-hoc meetings will be organized as needed [eg, to assess events of special interest or after receipt of a serious unexpected suspected adverse reaction (SUSAR)]. Specification details for the process and the outputs to be generated for eDMC review will be provided in the eDMC charter.

7.2. Interim Analyses and Summaries

The IA summaries will be a subset of the analyses described in this SAP, with the calculations of the observation period for a participant being based on the date of discontinuation or the date of the interim analysis data cut (ie, observation period = date of data cut [or conclusion date] – date of IP infusion + 1). Possible outputs include ABR, AIR, FVIII activity, safety, and other exploratory endpoints.

8. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AAV	Adeno-associated virus
AAV2/6	Adeno-associated vector 2/6
ABR	Annualized bleeding rate
AE	Adverse event
AESI	Adverse event of special interest
AIR	Annualized infusion rate
ATC	Anatomical Therapeutic Chemical
BE	Bleeding episode
BLoQ	Below the limit of quantification
BMI	Body mass index
bpm	Beats per minute
BU	Bethesda unit
cm	Centimeter
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
ELISA	Enzyme-linked immunosorbent assay
EQ-5D-5L	EuroQoL five dimensions, 5 levels questionnaire
F	Fahrenheit
FVIII	Factor VIII clotting protein
Gal3BP	Galectin-3-binding protein
Grp78	Glucose-regulated protein 78
IA	Interim analysis
IC	Informed consent
ICF	Informed consent form
IL6	Interleukin-6
IP	Investigational product
IU	International units
kg	Kilogram
LFT	Liver function test
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
mmHg	Millimeters of mercury
MRI	Magnetic resonance imaging
N/A	Not applicable

Abbreviation	Term
nAb	Neutralizing antibodies
PCR	Polymerase chain reaction
PT	Preferred term
rAAV	Recombinant adeno-associated viral vector
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
sEGFR	Soluble epidermal growth factor receptor
SoA	Schedule of Activities
SOC	System organ class
SUSAR	Serious unexpected suspected adverse reaction
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
vg	Vector genome
vWF	Von Willebrand Factor
WHO DD	World Health Organization Drug Dictionary