Protocol C3731003

Phase 3, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of PF-07055480 (Recombinant AAV2/6 Human Factor VIII Gene Therapy) in Adult Male Participants with Moderately Severe to Severe Hemophilia A (FVIII:C≤1%)

Statistical Analysis Plan (SAP)

Version: **6 (Final)**

Date: **12 Dec 2023**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
Version 1 4 Feb 2020	Original updated on 10 Dec 2019	N/A	N/A
Version 2 14 Apr 2021	Protocol Amendment 4 9 Apr 2021	Incorporated updates in Protocol Amendment 4.	See Summary of Changes Table in Protocol Amendment 4.
		Incorporated FDA's comments for the protocol and the SAP received on 19 Feb 2021.	• Added the description of alpha spending for the interim analysis and the primary analysis (Section 5.1). • Added hypothesis testing for ABR, steady state FVIII activity and AIR at the interim analysis (Section 5.1). • Updated the gatekeeping process with allocated alpha levels (Section 5.1).
		Additional changes made for clarity, completeness and consistency with Prococol Amendment 4 and the integrated analysis plan.	• Included definitions of treated bleed, untreated bleed and new bleed from the protocol and added the definition for a new untreated bleed (Section 3.1.1). • Added the algorithm to identify treated and untreated bleeds (Section 3.1.1). • Added a table for counting treated bleeding episodes toward overall ABR and ABR by location based on bleeding date/time and location (Section 3.1.1). • Added the 'Efficacy' population (Section 4). • Added the superiority test for mean FVIII activity at Week 52 compared to 5% in the gatekeeping process (Section 5.1). • Indicated pre-infusion data will include data collected during C0371004 up to preinfusion of PF-07055480 in C3731003 (Section 5.2). • Added three sensitivity analyses for ABR: using the first 6 months in the lead-in study and the last 6 months separately for pre-infusion observation period; using the alternative definition for new untreated bleeds for both ABR pre and postinfusion of PF-07055480 (Section 6.1.1.2).

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			• Added one sensitivity analysis that includes only bleeding and infusion data collected in C0371004 as comparison for ABR (Section 6.1.1.2), AIR (Section 6.2.2.2) and annualized FVIII consumption (Section 6.2.3). • Added summary of FVIII activity by visit and one-sample t-test to be done for Week 48, Week 52, Week 65, Week 78, and Week 104, as well as for Weeks 48-52 (Section 6.2.1.2). • Added box-and-whisker plots of FVIII activity by visit (Section 6.2.1.2). • Added imputation rules to handle missing item scores in calculating domain/component scores of Haem-A-QoL and HAL (Sections 6.2.9.1 and 6.2.9.2). • Updated the summary method for EQ-5D-5L (Section 6.3.1.3). • Added details for vector shedding analyses (Section 6.3.2). • Added a data listing for FVIII infusions post PF-07055480 infusion (Section 6.5.4). • Added a list of laboratory tests to be presented in shift tables and analyses for corticosteroid use (Section 6.6.2). • Added listings for PD related to COVID-19, SAE related to COVID-19 (Section 6.7). • Added a table for endpoints and analysis populations for the interim analysis (Section 7.2). • Updated HLIQ scoring (Appendix 1.4). • Added example SAS code for estimating percent reduction in mean ABR (Appendix 2.3). • Updated Appendix 3 Summary of Efficacy/PRO Analyses.

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Version 3 18 Jan 2022	Protocol Amendment 6 13 Jan 2022	Incorporated FDA's comments for the protocol and the SAP received on 24 Aug 2021.	• The interim analysis and alpha spending have been removed from the SAP (Section 2.2 and Section 2.3). • The timeframe of endpoints for the primary analysis is changed to 15 months (corresponding study visit at Week 65 weeks) postinfusion (Section 2.2 and Section 2.3). • The time period for Year 2 changed to from > 15 months to 24 months for FVIII activity assessment (Section 3.2.1). For bleeding and FVIII infusion/consumption, Year 2 time period is changed to > Day 455 through Day 730 (Section 3.1.1). • The key secondary endpoint is changed from the steady state FVIII activity to FVIII activity level > 5% at 15 months postinfusion (Section 2.2.2 and Section 3.2.1). • The percentage of participants with FVIII activity level > 5% at 15 months postinfusion will be tested against the null hypothesis of percentage ≤ 68% using a one-sided exact binomial proportion test (Section 6.2.1.1). • The onset of FVIII activity steady state will be considered as Week 12 (Section 2.3). • The calculation of steady state FVIII activity level is updated to incorporate the change in the onset of steady state as a geometric mean of all eligible FVIII:C measures from Week 12 through 15 months after PF-07055480 infusion. The steady state FVIII activity will be reported with descriptive statistics and 95% CI of mean without performing hypothesis testing (Section 6.2.4). • Total ABR (treated and untreated bleedings) from Week 4 [Day 22] through 15 months following PF-07055480 infusion is changed to be the other key secondary endpoint and will be compared to preinfusion of PF-07055480 (under SOC FVIII prophylaxis replacement regimen) and analyzed separately using the same method applied to treated ABR (Section 3.1.1). • The gatekeeping sequence is updated in accordance with the changes in the key secondary endpoints (Section 5.1).

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		Additional changes made for clarity, completeness and consistency with Prococol Amendment 6 and the integrated analysis plan.	• Updated the calculation for the estimate of percent reduction in mean AIR (Section 6.2.3.1). • Removed one AIR sensitivity analysis for excluding perioperative infusions (Section 6.2.3.2). • Summary for HLIQ data is changed to counts and percentage for response score in each individual question by visit. No total score will be calculated since total score is not meaningful (Section 6.3.1.1). • Summary for target joints has been updated to report number and percentage of participants with 0, 1, 2 or ≥3 target joints at specified timepoints and summary of change from baseline is removed (Section 6.3.4.1).
Version 4 1 Jul 2022	Protocol Amendment 7 26 May 2022	Incorporated updates in Protocol Amendment 7 based on the regulatory request	• The ABR primary efficacy endpoint has been revised to be Total ABR (including treated and untreated bleeds). The ABR (treated bleeds) is now part of the key secondary endpoints (Section 2.2, Section 3.1.1, and Section 3.2.2). • The assessment of all endpoints related to bleeds and infusions (including Total ABR, Treated ABR, AIR and annualized FVIII consumption) will start from 12 weeks post study drug infusion (instead of 4 weeks), corresponding to the estimated FVIII activity level steady state onset (Section 2.2). • Updated the order of testing sequence in the gatekeeping process due to changes in the primary and key secondary endpoints (Section 5.1). • Addition of the summary for the percentage of participants with FVIII activity levels ≥40% by visit (Section 6.2.5).
		Additional changes made for clarity, consistency, and completeness	• Updated the assessment of corticosteroid use with additional definition details (Section 6.5.4). • Added the imputation rule for FVIII activity levels after participants have resumed prophylaxis regimen (Section 3.2.4 and Section 3.2.5).

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			• Removed questionnaires of HEAD-US, Haem-A-QoL and HLIQ from appendices (Section 9).
Version 5 12 Apr 2023	Protocol Amendment 9 3 Feb 2023	Incorporated updates in Protocol Amendment 9	• Increased the sample size from 63 to 70 (Section 2.3). • Added endpoints and data reporting for optional liver biopsy substudy (Section 2.2). • Updated the definition of 'Efficacy' population (Section 4). • Changed the main analysis population from 'Dosed' population to 'Efficacy' population (Section 6). • Added summary tables of Total ABR (Section 6.1.1.2), Treated ABR (Section 6.2.2.2), percentage of participants without bleeds (Section 6.2.9), and AIR (Section 6.2.3.2) for participants dosed with nominal concentration in the 'Dosed' population. • Added a summary of FVIII activity by threshold category (e.g., <1%, 1-5%, >5-<15%, 15-<40%, 40-150%, >150%) by selected visit for participants dosed with nominal concentration in the 'Dosed' population (Section 6.2.1.2). • Added summary tables of adverse events for participants dosed with nominal concentration in the 'Dosed' population (Section 6.6.1). • Added summary tables of demographic and baseline characteristics separately for the 'Efficacy' population and participants dosed with nominal concentration in the 'Dosed' population (Section 6.5.1).
		Alignment with regulatory feedback on another Pfizer hemophilia gene therapy product	• Added additional sensitivity analyses for Total ABR: including data up to data cutoff and applying imputation rules for taking FVIII infusion, resumption of prophylaxis regimen, or study discontinuation (Section 6.1.1.2). • Added summary of follow-up duration (in days) following cessation of the latest corticosteroid therapy in the participants who received corticosteroid (Section 6.5.4).

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		Alignment with FDA's advice received in April 2022	• Added summary of corticosteroid treatment cycles (Section 6.5.4).
		Additional changes made for clarity, consistency, and completeness	• Updated the population attribute in estimands by removing 'not on FVIII prophylaxis regimen' since resumption of FVIII prophylaxis has been included in the intercurrent event attribute (Section 2.2.1 and Section 2.2.2). • Updated the analysis visit window for FVIII activity at Week 65 from Weeks 59-71 to Weeks 63-67 in order to include data closer to the target time point of Week 65 (Section 3.2.1). • Added a sensitivity analysis to summarize FVIII activity by threshold category by selected visit in the 'Efficacy' population (Section 6.2.1.2). • Added imputation rules for missing FVIII activity in the Week 65 visit window (Section 3.2.1). • Updated Table 7 for counting new bleeds occurring on the same date based on bleeding time, location type, and bleeding site (Section 3.1.1). • Added a description for the further validated assays and identifying appropriate FVIII activity data to be included in analysis and summary (Section 3.2.1). • Updated the domain names in Haem-A-QoL (Section 3.2.11.1). • Named the group of participants who participated in the optional substudy for X-ray assessments as the Joint X-Ray Substudy (Section 5). • Added summary of cumulative prednisone-equivalent dose for corticosteroid treatment and average daily prednisone-equivalent dose per participant (Section 6.5.4). • Added a rule to combine corticosteroid courses in order to identify corticosteroid escalation before/during weaning (Section 6.5.4). • Added the summary of AEs related to corticosteroid treatment as deemed by the investigator (Section 6.6.1).

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			• Added exclusion of FVIII antigen data after resumption of prophylaxis regimen (Section 3.3.3.1). • Added the instruction when there are two FVIII inhibitor results (one from assay with DOAC reversal agent and one without) at the same visit, the result with DOAC reversal agent should be used (Section 3.2.1). • Added supplementary analyses of Total ABR and Treated ABR by cause x location (Section 6.2.8 and Section 6.2.7). • Removed vector shedding spaghetti plots; added for the individual plot, BLoQ value to be imputed as one half of the LLoQ value for plotting purposes (Section 6.3.2). • Removed summaries of TEAEs and SAEs during the first 15 months since there are such summaries for the entire study period and during the first 2 years (Section 6.6.1). • Updated the description of the ultrasound substudy and the vector shedding substudy (Section 4).
Version 6 12 Dec 2023	Protocol Amendment 10 28 Sep 2023	Further alignment with regulatory feedback on other hemophilia gene therapy products	• Updated the data to be included for the ABR/AIR-related endpoints of the primary analysis from "through 15 months postinfusion" to "at least 15 months (up to data cutoff) postinfusion" (Section 2.2). • Updated the variable attribute in the primary estimand for Total ABR and the secondary estimand for Treated ABR accordingly (Section 2.2.1 and Section 2.2.2). • Updated the sensitivity analysis for Total ABR (Section 6.1.1.2), Treated ABR (Section 6.2.2.2), AIR (Section 6.2.3.2) and annualized FVIII consumption (Section 6.2.6) on the 'Dosed' population (regardless of the follow-up length in the preinfusion or postinfusion period) by including all prospectively collected data in the lead-in study instead of the retrospective data. • Removed the sensitivity postinfusion summary of Total ABR (Section 6.1.1.2), FVIII activity (Section 6.2.1.2), Treated

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			ABR (Section 6.2.2.2), AIR (Section 6.2.3.2), and percentage of participants without bleeds (Section 6.2.9) for participants who were dosed with nominal concentration since a sensitivity analysis based on the 'Dosed'' population has been added. • Added a data listing for the assessment of treatment failure (Section 6.1.1.3). • Updated the sensitivity and supplementary analyses of FVIII activity to use the 'Dosed' population (Section 6.2.1.2 and Section 6.2.5). • Updated exclusion of FVIII activity and FVIII antigen data for any sample taken within 72 hours after administering exogenous FVIII replacement therapy products with standard half-life or 120 hours for products with extended half-life, for any purpose (including treatment of bleeding or prevention purposes) to be excluded from analysis/summary (Section 3.2.1). • Updated the imputation rules for missing FVIII activity data (Section 3.2.1, Section 3.2.4 and Section 3.2.5). • Added a summary of FVIII activity at Weeks 26, 52, 65, 104 and 156 with order statistics (Section 6.2.5). • Updated the definition of corticosteroid (CS) courses, removed CS cycles, and added summary of the entire duration on corticosteroids (Section 6.5.4).
		Additional US-specific analyses aligned to regulatory requests (in Appendix 1.4)	• Added a supplementary analysis for Total ABR with imputation rules for the event of prophylaxis resumption and/or taking FVIII infusion in a manner similar to prophylaxis post PF-07055480 infusion in the observation period before data cutoff and using the 'Dosed' population (regardless of the follow-up length in the preinfusion or postinfusion period) (Section 9, Appendix 1.4).

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			• Added a sensitivity analysis of Total ABR from Week 12 through at least 15 months postinfusion with imputation rules for the event of prophylaxis resumption and/or taking FVIII infusion in a manner similar to prophylaxis post PF-07055480 infusion in the observation period before data cutoff and using the 'Efficacy' population (Section 9, Appendix 1.4).
		Additional changes made for clarity, consistency, and completeness	• Extended the visit window of HJHS/PRO endpoints at Month 12 to avoid missing data at this timepoint (Section 6.2.11).

2. INTRODUCTION

Gene therapy approaches in hemophilia A have been historically constrained by the large size of human factor VIII (hFVIII) gene, the high adeno-associated virus (AAV) dose required to achieve therapeutic coagulation factor VIII (FVIII) levels, and the low manufacturing yields of AAV hFVIII. PF-07055480 has a shorter coding sequence for hFVIII B-domain deleted (BDD), an optimized, robust liver-specific promoter module to drive hFVIII expression, and improved virus yields. PF-07055480 is designed to require only a single administration into hemophilia A individuals, eliminating the disease burden associated with the condition and its treatment.

C3731003 pivotal Phase 3 study will further evaluate the clinical efficacy and safety of PF07055480 in adult male participants with moderately severe to severe hemophilia A (FVIII:C≤1%) for 5 years after a single administration of the study intervention at the dose of 3×10^{13} vg/kg, compared to routine prophylaxis with FVIII products. The study will enroll approximately 70 eligible participants from Study C0371004 to achieve at least 50 dosed participants who complete at least 15 months of follow-up postinfusion in this study (C3731003) (i.e., the data cutoff for the primary analysis). These 50 participants will have completed at least 6 months of routine prophylaxis follow-up in Study C0371004. The duration of follow up in the lead-in study (C0371004) may be shorter than 6 months after at least 50 hemophilia A participants are expected to reach 15 months postinfusion in C3731003.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C3731003. 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.

Deviations from this analysis plan will be described in the Clinical Study Report (CSR), if any.

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APPENDICES

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2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives, Endpoints, and Estimands

The study objectives are presented in Table 2 below with corresponding endpoints.

Table 2. Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy Objective	**Primary Endpoint and Key Secondary Endpoint**
• Evaluate the efficacy of a single infusion of PF-07055480 in participants ≥18 and <65 years of age with moderately severe to severe hemophilia A (FVIII C ≤ 1%).	**Primary Endpoint:** • Total annualized bleeding rate (ABR) (spontaneous and traumatic bleedings, treated and untreated) from Week 12 through at least 15 months following PF-07055480 infusion versus Total ABR on prior FVIII prophylaxis replacement regimen. **Key Secondary Endpoints:** • FVIII activity level >5% at 15 months following infusion of PF-07055480. • ABR (spontaneous and traumatic treated bleedings) from Week 12 through at least 15 months following PF-07055480 infusion versus ABR on prior FVIII prophylaxis replacement regimen.
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints**
• To demonstrate that the use of exogenous FVIII is significantly reduced post PF-07055480 infusion.	• Annualized infusion rate (AIR) of exogenous FVIII from Week 12 through at least 15 months following infusion of PF-07055480 versus AIR on prior FVIII prophylaxis replacement regimen.
• To assess additional efficacy parameters post PF-07055480 infusion including FVIII activity level, use of exogenous FVIII, information on bleeding events and patient reported outcomes (PROs).	• FVIII activity level from Week 12 through 15 months following infusion of PF-07055480. The following secondary parameters will be assessed from Week 12 through at least 15 months after PF-07055480 infusion and

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Objectives	Endpoints

	compared with prior FVIII prophylaxis replacement regimen:
	• Annualized FVIII consumption.
	• Treated ABR of specific type:
	  o by cause (spontaneous or traumatic)
	  o by location (in joints, in target joints, or in soft tissue).
	• Total ABR by cause and by location.
	• Percentage of participants without bleeds.
	The following secondary parameters will be assessed by visit after PF-07055480 infusion:
	• FVIII activity level.
	• Change from baseline in joint health as measured by the Hemophilia Joint Health Score (HJHS) instrument.
	• Change from baseline in the following PRO endpoints:
	  o Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)
	  o Haemophilia Activities List (HAL)

• Estimate the durability of efficacy up to 5 years after PF-07055480 infusion.	The following parameters will be analyzed yearly or by visit as appropriate: • Treated ABR. • FVIII activity level. • AIR of exogenous FVIII. • Annualized FVIII consumption. • Treated ABR of specific type: o by cause (spontaneous or traumatic).

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Objectives	Endpoints
	○ by location (in joint, in target joints, or in soft tissue). • Total ABR. • Total ABR by cause and by location. • Percentage of participants without bleeds. • Change from baseline in joint health as measured by the HJHS instrument. • Change from baseline in PRO endpoints: Haem-A-QoL and HAL. In addition, Treated ABR, Total ABR, and AIR will be analyzed throughout the 5-year study period.
Secondary Safety Objective	**Secondary Safety Endpoints**
• To estimate the safety and tolerability of PF-07055480, including immunogenicity, for the study duration of 5 years after PF-07055480 infusion.	• Incidence and severity of adverse events (AEs). • Events of special interest (such as hypersensitivity reactions, clinically reported thrombotic events, and malignancy). • Immunogenicity: ○ Antibodies against adeno associated viral vector, serotype 6 (AAV6) capsid protein (neutralizing antibodies [nAbs] and anti-drug antibodies [ADAs]). ○ T-cell responses against AAV6 capsid and against the transgene. ○ FVIII inhibitors.
Tertiary/Exploratory	
• To evaluate vector shedding and infectivity in body fluids.	Vector shedding and infectivity of PF-07055480 in plasma, saliva, peripheral blood mononuclear cells (PBMC), urine, and semen until negative on 3 consecutive occasions for each specimen type.

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Objectives	Endpoints
• To evaluate exploratory pharmacodynamic biomarkers.	• FVIII antigen levels. • Von Willebrand factor.
• To compare joint health post PF-07055480 infusion to baseline and evaluate long-term joint outcomes.	• Number of target joints. • Joint status as assessed by X-ray. • Joint status as assessed by ultrasound.
• To evaluate for any effects on coagulation.	• Coagulation activation tests: activated partial thromboplastin time (aPTT), international normalized ratio (INR), D-dimer, thrombin generation assay (TGA), and thrombin antithrombin level (TAT). • Comparison of FVIII activity between one stage assay and chromogenic assay. • Recovery of FVIII products post gene therapy.
• To further compare PF-07055480 on PROs addressing health-related quality of life, activities of daily living and general health status.	The following PRO instruments will be compared with FVIII replacement regimen, using comparisons pre and postinfusion of PF-07055480 through 12 months and annually during the follow-up period: • Hemophilia Life Impacts Questionnaire (HLIQ). • EuroQol, 5 dimensions, 5 levels (EQ-5D-5L).
• To further evaluate PF-07055480 mechanism of action and immune responses.	• Cellular immunity by cell-mediated assays. • Binding immunoglobulin G (IgG) versus immunoglobulin M (IgM) assay. • Other biomarkers as inflammatory cytokines.
• To evaluate the cross reactivity between AAV serotypes.	nAbs against other AAV serotypes.
Optional liver biopsy substudy only: • To evaluate vector integration in the liver	• For the integrations analyses (as feasible): the number and location of integration sites, the location of the integration sites relative to transcription start sites, the nature of the

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Objectives	Endpoints
• 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	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 (e.g., presence of fibrosis assessment, presence of lymphocytic invasion), protein and/or ribonucleic acid (RNA) expression of FVIII and selected biomarkers (e.g., glucose regulatory protein 78 [Grp78], galectin-3-binding protein [Gal3BP]).

2.2.1. Primary Estimand

The primary estimand is the treatment effect of PF-07055480 compared to routine prophylaxis with respect to Total ABR (treated and untreated bleeds) after prior prophylaxis treatment is stopped following infusion, from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion.

The corresponding estimand attributes are provided in Table 3 below.

Table 3. Attributes of Primary Estimand

Estimand Attribute	Description
Population	Male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII:C ≤1%), who have tested negative for anti-AAV6 nAb and have no medical history of FVIII inhibitor.
Variable	Total ABR (treated and untreated bleedings) from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF-07055480 infusion.
Intercurrent Event	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation will not be imputed.
Population-Level Summary	Total ABR post PF-07055480 infusion will be compared to participants' Total ABR on prior FVIII prophylaxis regimen using a repeated measure negative binomial regression model. Model-based estimated difference in mean Total ABR and the 95% CI will be reported. In addition, percent reduction in mean Total ABR and the corresponding 95% CI will be estimated.

Because no more than a single dose of study intervention will be administered during the study, there should be no treatment discontinuations. If it is determined by the investigator that a participant should resume routine prophylaxis post PF-07055480 infusion, date and

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reason of investigator decision to resume FVIII prophylaxis will be collected in the eCRF, and this date will be considered as the date of FVIII prophylaxis resumption.

2.2.2. Secondary Estimands

The secondary estimands are the treatment effect of PF-07055480 with respect to FVIII activity level > 5% at 15 months postinfusion and the treatment effect compared to routine prophylaxis with respect to Treated ABR after prior prophylaxis treatment is stopped following infusion, from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion. Throughout the SAP '15 months' corresponds to '65 weeks' for analysis purposes.

The secondary estimands include the following 4 attributes as described in Table 4 and Table 5 below.

Table 4. Attributes of Secondary Estimand –FVIII activity level > 5%

Estimand Attribute	Description
Population	Male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII:C ≤1%), who have tested negative for anti-AAV6 nAb and have no medical history of FVIII inhibitor.
Variable	FVIII activity level > 5% at 15 months (65 weeks) post PF-07055480 infusion.
Intercurrent Event	• Any sample taken within 72 hours for standard half-life or 120 hours for extended half-life products after administering exogenous FVIII replacement therapy for any purpose (including treatment of bleeding or prevention purposes) will be excluded from the assessment of FVIII activity post PF-07055480 infusion. • Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. Participants who resume prophylaxis regimen prior to Month 15 postinfusion will be considered as having FVIII activity level ≤5%. • Participants who discontinue from the study before Month 15 will be considered as having FVIII activity level ≤5%.
Population-Level Summary	The percentage of participants with FVIII activity level > 5% will be calculated and compared with the null hypothesis of percentage ≤ 68% using an exact test for binominal proportion.

Table 5. Attributes of Secondary Estimand - Treated ABR

Estimand Attribute	Description
Population	Male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII:C ≤1%), who have tested negative for anti-AAV6 nAb and have no medical history of FVIII inhibitor.
Variable	Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF-07055480 infusion.

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Estimand Attribute	Description
Intercurrent Event	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation will not be imputed.
Population-Level Summary	Treated ABR post PF-07055480 infusion will be compared to participants' Treated ABR on prior FVIII prophylaxis regimen using a repeated measures negative binomial regression model. Model-based estimated difference in mean Treated ABR and the 95% CI will be reported. In addition, percent reduction in mean Treated ABR and the corresponding 95% CI will be estimated.

2.2.3. Additional Estimands

Not applicable.

2.3. Study Design

Study C3731003 is a Phase 3, open-label, multicenter, single arm study to evaluate the efficacy and safety of a single infusion of PF-07055480 in adult male participants with moderately severe to severe hemophilia A (FVIII:C ≤1%).

Eligible study participants will be followed while on routine FVIII prophylaxis therapy in the lead-in Study C0371004 in order to collect pretreatment (established usual care) data for efficacy and selected safety parameters.

This study will include an approximately 6-week screening (screening can be extended beyond 6 weeks when needed) and baseline period followed by the dosing day (Day 1), a 2-year efficacy and safety observation period (short term monitoring), and a 3-year long-term monitoring period.

This study will enroll approximately 70 eligible participants from Study C0371004 to achieve at least 50 dosed participants who complete at least 15 months of follow-up postinfusion in this study (C3731003). These 50 participants will have completed at least 6 months of routine prophylaxis follow up in Study C0371004. The duration of follow up for subsequent participants in the lead-in study (C0371004) may be shorter than 6 months after at least 50 hemophilia A participants are expected to reach 15 months postinfusion in this study (C3731003). The study design is displayed in Figure 1 below.

The primary analysis will be conducted when at least 50 dosed participants have reached at least 15 months of follow-up postinfusion, corresponding to at least 12 months of follow-up for these 50 dosed participants after the estimated FVIII activity steady state onset. The onset of FVIII activity steady state based on the C3731001 study data is expected to be reached at the beginning of Week 9 postinfusion. However, as a conservative approach, the beginning of steady state will be considered as Week 12 (i.e., approximately 3 months) for the primary analysis.

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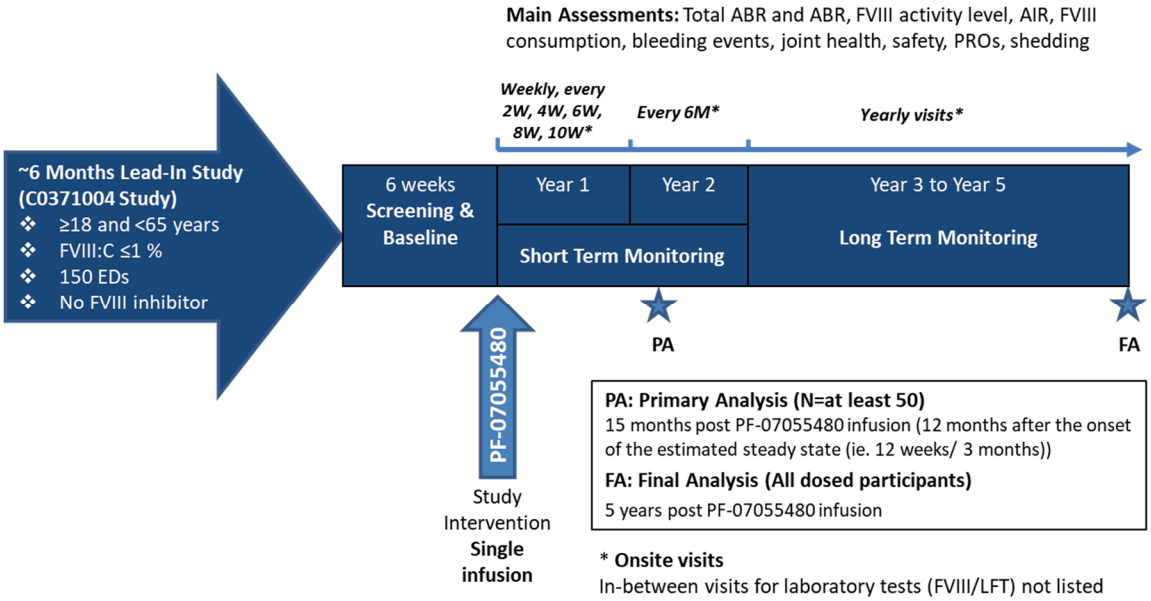
A final analysis will be conducted when all dosed participants have completed the entire study (i.e., 5 years in follow-up duration per participant) or discontinued prematurely from the study.

The study may be paused in the event of a confirmed inhibitor level or a thrombotic event suspected to be related to > upper limit of normal (ULN) for FVIII activity levels for a participant as described in the Protocol Sections 8.1.2.3 and 8.2.6.2.

If the decision to pause the study is made, no additional participant will be treated until the circumstances for such an event are assessed and regulatory agencies are notified, if required. If paused, the trial re-start will only be possible after Regulatory Authority approval via substantial amendment, where applicable based on local/regional regulatory requirements.

Figure 1. C3731003: Study Design



3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

The primary efficacy endpoint will be the Total ABR (including both treated and untreated bleeds) from Week 12 [Day 78] through at least 15 months of follow up, following infusion of PF-07055480 versus Total ABR while on FVIII prophylaxis replacement regimen prior to infusion of PF-07055480.

3.1.1. Total Annualized Bleeding Rate (Total ABR)

An eDiary, a handheld device, will be provided to all participants on Visit 1. Participants are required to enter any occurrence of hemophilic bleeding episodes (including date, time,

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location, and etiology) and any exogenous FVIII replacement (including date, time, reason, and dose) required to treat the bleeds in the eDiary.

Definitions of bleeds are provided below.

Treated Bleed: An event necessitating administration of coagulation factor within 72 hours of signs or symptoms of bleeding (protocol definition, unless specifically referring to untreated bleed).

Untreated Bleed: A bleeding event not necessitating administration of coagulation factor within 72 hours of signs and symptoms of bleeding.

New Bleed:

- A '**new treated bleed**' is a bleed necessitating treatment (as described above) occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated or a bleed necessitating treatment (as described above) occurring at a different site from the original bleed regardless of the time from last injection.
- A bleed is considered a '**new untreated bleed**' if it does not necessitate treatment and occurring >72 hours after the previous untreated bleed at the same site or occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated, or an untreated bleed occurring at a different site from the original bleed regardless of the time from last bleed or last injection.

If a bleed is treated with FVIII infusion (as indicated in the bleeding log of the eDiary) within 72 hours (by comparing date/time of bleeding to date/time of infusion in the eDiary), regardless of the type of treatment (preventive, prophylaxis or on demand), it will be considered as a treated bleed. If a bleed is not treated with FVIII infusion, as indicated in the eDiary bleeding log, the bleed will be considered as an untreated bleed. Table 6 provides a summary of bleeds that are considered treated/untreated bleeding events based on the data captured within the eDiary.

Table 6. Treated Bleeds / Untreated Bleeds Based on eDiary Data

Factor infusion was used to treat the bleed? (reported in eDiary bleeding log)	Any FVIII infusion within (≤) 72 hours post bleeding?	Treated/Untreated bleed
Yes	Yes (regardless of reason)	Treated bleed
Yes	No	Untreated bleed
No	Yes (regardless of reason)	Untreated bleed
No	No	Untreated bleed

Only new bleeds will be counted toward the number of bleeds for ABR calculation. New bleeds that occurred on the same date will be counted using the following algorithm to derive overall bleeds and bleeds by location type as displayed in Table 7 below.

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Table 7. Counting New Bleeds Occurring on the Same Date Based on Bleeding Time, Location Type, And Bleeding Site

Multiple new bleeding episodes occurring (regardless spontaneous or traumatic) on the same date	Same location type	Same bleeding site*	Counting toward overall bleeds	Counting toward bleeds by location type
Same date/time	Yes	No	One bleeding episode	One bleeding episode at the given location type
Same date/time	No	No	One bleeding episode	One bleeding episode for each location type
Same date but different time	Yes	No	Separate bleeding episodes	Separate bleeding episodes at the given location type
Same date but different time	No	No	Separate bleeding episodes	One bleeding episode for each location type

Note: Location type refers to joint and soft tissue/muscle/other. Bleeding site refers to the body location (e.g., left/right shoulder, left/right knee, left/right arm, etc.).
*Per the definition of new bleeds, there won't be multiple new bleeds occurring at the same bleeding sites on the same date.

The number of treated and untreated bleeding episodes from Week 12 [Day 78] through data cutoff (at least 15 months) after PF-07055480 infusion will contribute to the postinfusion Total ABR calculation of each participant, which is considered the primary endpoint. Total ABR during additional time periods postinfusion (as indicated below) will be analyzed as secondary endpoints. The following yearly intervals as well as cumulative follow-up intervals will be used for reporting Total ABR data postinfusion. Note: here and throughout, Year 2 summaries include data following Month 15 (Day 455) through Month 24 (Day 730).

Yearly Interval	Interval Derivation
Month 15	Day 77 < Month 15 ≤ Day 455
Year 2	Day 455 < 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

Note: Day 1 is the day when PF-07055480 infusion started.

Cumulative follow-up interval	Interval Derivation
Cumulative follow up through 2 years postinfusion	Day 78 to Day 730
Cumulative follow up through 3 years postinfusion	Day 78 to Day 1095
Cumulative follow up through 4 years postinfusion	Day 78 to Day 1460
Cumulative follow up through 5 years postinfusion	Day 78 to End of the study

For participants with incomplete data for the entire yearly time period, including participants who discontinued, all data during the specified period will be annualized and summarized utilizing the number of days of follow-up during the given time period (i.e., observation period). Total ABR for each participant will be calculated as below:

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Total ABR =

$$\frac{\text{(Number of treated and untreated bleeding episodes during the given time period)} \times 365.25}{\text{(Number of days of follow-up in the given time period)}}$$

Data before Week 12 postinfusion are excluded to account for the potential differences in participants' pharmacokinetics postinfusion. As a result, the denominator in the above calculation for the Month 15 and cumulative follow-up intervals will be [the last date in the given time period – (Date of PF-07055480 infusion) – 77 days +1].

For the primary endpoint assessment of Total ABR from Week 12 through at least 15 months (up to data cutoff), the number of bleeds post resumption of prophylaxis regimen or study discontinuation will be excluded. As a result, the denominator (i.e., number of days in the observation period) in the above Total ABR calculation will include days up to data cutoff, the day before resumption of prophylaxis regimen, or discontinuation date, whichever occurs earliest.

Total ABR during yearly intervals and cumulative follow-up intervals are considered as secondary endpoints. If the participant discontinues from study before the end of the prespecified observation period, the last date in the given observation period will be the date of study discontinuation. In addition, if FVIII prophylaxis regimen is resumed for a participant as defined in Protocol Section 6.5.1 then data collected on and after the date of prophylaxis resumption entered in the eCRF by the investigator will be excluded from the calculation of Total ABR by interval, which means the bleeding events will be excluded and the corresponding time period will be deducted as well.

Total ABR prior to PF-07055480 will be calculated using all treated and untreated bleeds documented during the lead-in study (C0371004) up to preinfusion of PF-07055480 and the respective number of days of follow-up within the lead-in study and preinfusion period using the same formula presented above.

3.2. Secondary Endpoints

3.2.1. Key Secondary Endpoint: Factor VIII Activity > 5% at 15 Months Postinfusion

Samples to assess circulating factor VIII 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 assay.
- In local laboratories, FVIII activity will be assessed by chromogenic or one-stage clotting assay based on standard practice.

Primary and secondary objectives are based on the chromogenic assay results from the central laboratory. Central chromogenic assay results will be used as the primary FVIII activity measurement as this approach is considered the most conservative because it resulted in the lowest activity levels in the Phase 1b/2 study (C3731001).

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In 2022, FVIII activity assays were validated to an extended upper limit of quantification (ULoQ) and to neutralize the effect of direct oral anticoagulant (DOAC) for participants treated by DOAC. These further validated assays have been implemented by the central laboratory since 15 June 2022. As such, the back-up of samples assessed before this date and corresponding to these criteria (i.e., the initial result was above the ULoQ or the participant was on DOAC at the time of sample collection) have been retested. As a result, when applicable, the initial FVIII activity levels will be replaced by the appropriate retested levels and the later will be included in the summary/analysis.

Following the implementation of further validated assays, only the following FVIII activity levels listed below will be considered as appropriate and included in the statistical analysis and summary.

- FVIII activity results with DOAC reversal agent if the participant was on DOAC at the time of sample collection.
- FVIII activity results without DOAC reversal agent if the participant was not on DOAC at the time of sample collection.

In addition, the initial FVIII activity results collected prior to the further assay validation that did not require retesting will also be considered as 'appropriate' and included in the analysis and summary.

For completeness, all FVIII activity results (from initial and retested samples) will be included in data listings.

Any sample taken within 72 hours for standard half-life products or 120 hours for extended half-life products after administering exogenous FVIII replacement therapy for any purpose (including treatment of bleeding or prevention purposes) will be excluded. When multiple appropriate FVIII activity observations are collected on the same day for a participant, the average level of these observations will be used for the given day. Additionally, any FVIII activity levels after the resumption of FVIII prophylaxis regimen (if necessary) will be replaced with 0.9% for analysis purposes, and therefore considered as having FVIII activity ≤ 5%. FVIII activity collected at unscheduled visits will be mapped to a visit if the data collection date falls into the protocol-defined visit window.

Participants who prematurely discontinue from the study prior to reaching Month 15 visit will be considered as having FVIII activity ≤ 5% for the main analysis of this endpoint.

The FVIII activity level at 15 months post PF-07055480 infusion will include all appropriate FVIII activity data collected around the Week 65 visit (from Week 63 through Week 67), including unscheduled visit observations. In a case when multiple observations fall into the same visit window, an average FVIII activity level will be taken over these observations and included in the analysis.

For participants who have not discontinued from the study before Week 65 visit and have not resumed prophylaxis, if there are no appropriate FVIII activity levels for a participant in the main analysis population during the visit window of Week 65 visit (from Week 63 through

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Week 67), the missing FVIII activity level will be imputed with the earliest appropriate FVIII activity level collected post Week 65 visit window. In case there are no appropriate FVIII activity levels post Week 65 visit window, the FVIII activity at Week 65 will be considered as missing and excluded from the assessment.

3.2.2. Key Secondary Endpoint: Treated ABR

Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) following PF-07055480 infusion is considered as another key secondary endpoint. The data collection and endpoint derivation are similar to those described for Total ABR in Section 3.1.1. In addition, Treated ABR will be reported by yearly interval as well as by cumulative follow-up interval after PF-07055480 infusion as secondary endpoints.

3.2.3. Annualized Infusion Rate (AIR) of Exogenous FVIII

AIR of exogenous FVIII replacement following PF-07055480 infusion from Week 12 [Day 78] through at least 15 months (up to data cutoff) after PF-07055480 infusion is considered as a secondary endpoint and will be compared with AIR during prior FVIII prophylaxis replacement regimen.

All infusions during the observation time period for any purpose (to treat bleeding, for preventive purpose, perioperative, or if FVIII prophylaxis regimen is resumed) will be included in the calculation of AIR. AIR data after PF-07055480 infusion will additionally be analyzed for the yearly intervals as well as cumulative follow-up intervals as separate secondary endpoints.

For participants with incomplete data for the entire yearly time period, including participants who discontinued prior to completing the study, all data during that period will be annualized and summarized utilizing the number of days of follow-up during the given time period. AIR for each participant will be calculated as below:

$$\text{AIR} = \frac{(\text{Number of infusions for any purpose during the given time period}) \times 365.25}{(\text{Number of days of follow-up in the given time period})}$$

Same as explained in Section 3.1.1, the follow-up period will exclude the first 11 weeks (77 days). The denominator in the above calculation for postinfusion up to data cutoff, Month 15 interval and cumulative follow-up intervals will be [the last date in the given time period – (Date of PF-07055480 infusion) – 77 days +1]. If the participant discontinues from study before the end of the prespecified time period, the last date in the given time period will be the date of study discontinuation.

If a participant has to resume FVIII prophylaxis treatment, prophylaxis FVIII infusion data will not have to be reported on the eDiary (or conveyed to the study site staff on a contemporaneous basis) after Week 78 (Month 18). The eDiary will continue to collect bleeds and non-prophylactic infusions (e.g., on-demand and preventative) throughout the course of the study. The prophylaxis infusion data will be derived from the prescribed FVIII product information and included in the AIR calculation.

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The AIR data collected in the lead-in study (C0371004) while participants were on the FVIII prophylaxis replacement regimen up to the time period prior to PF-07055480 infusion in this study will be annualized using the same formula presented above and used for comparison. During this study, all infusions from Week 12 [Day 78] will be included in the AIR calculation including those to treat bleeding (on-demand), for prophylaxis, for preventive purposes, or perioperative infusions.

3.2.4. FVIII Activity Level from Week 12 through 15 Months Postinfusion

The beginning of steady state will be considered as Week 12 for analysis purposes within this Phase 3 study. Additionally, the data from this Phase 3 study will be utilized to confirm the timing of the onset of steady state.

The Factor VIII activity from Week 12 through 15 months postinfusion will be calculated for each participant as a geometric mean of all appropriate FVIII activity measures (including unscheduled visit observations) from Week 12 through 15 months (up to the upper bound of the Month 15 visit window: Week 67) after PF-07055480 infusion based on central chromogenic assay and one-state clotting assay separately. When multiple appropriate FVIII activity observations are collected on the same day for a participant, the average level of these observations will be used for that given day. FVIII activity will be imputed with 0.9% after the participants have resumed prophylaxis regimen up to data cutoff or Week 67, whichever occurs earlier.

If a participant has missing data for a study visit or has otherwise discontinued due to any reasons other than lack of efficacy but has not resumed prophylaxis prior to completing the designated follow-up period, all available data will be included to calculate geometric mean despite the missed measurements. Specifically, imputation of FVIII activity will be applied per scenarios listed below:

- Resumed prophylaxis but remained in the study: Impute FVIII activity with 0.9% at any protocol-defined visits post resumption of prophylaxis until data cutoff or Week 67, whichever occurs earlier.

- Resumed prophylaxis and then discontinued from the study due to any reasons: Impute FVIII activity with 0.9% at any protocol-defined visits post resumption of prophylaxis until data cutoff or Week 67, whichever occurs earlier.

- Discontinued from study due to lack of efficacy but has not resumed prophylaxis: Impute FVIII activity with 0.9% at any protocol-defined visits post study discontinuation until data cutoff or Week 67, whichever occurs earlier.

- Discontinued from the study due to any reasons other than lack of efficacy but has not resumed prophylaxis: No imputation will be applied. FVIII activity after study discontinuation will be considered missing.

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3.2.5. FVIII Activity Level by Visit

Mapping for unscheduled visit observations and exclusion in FVIII activity data are described in Section 3.2.1. FVIII activity analyzed by the central laboratory will be reported for chromogenic assay and one-state clotting assay separately. FVIII activity will be imputed with 0.9% through data cutoff after the participants have resumed prophylaxis regimen and after they discontinued from the study due to lack of efficacy. FVIII activity won't be imputed after participants discontinue from the study due to reasons other than lack of efficacy if they have not resumed prophylaxis. Specifically, imputation of FVIII activity will be applied per scenarios listed below:

- Resumed prophylaxis but remained in the study: Impute FVIII activity with 0.9% at any protocol-defined visits post resumption of prophylaxis until data cutoff.
- Resumed prophylaxis and then discontinued from the study due to any reasons: Impute FVIII activity with 0.9% at any protocol-defined visits post resumption of prophylaxis until data cutoff.
- Discontinued from study due to lack of efficacy but has not resumed prophylaxis: Impute FVIII activity with 0.9% at any protocol-defined visits post study discontinuation until data cutoff.
- Discontinued from the study due to any reasons other than lack of efficacy but has not resumed prophylaxis: No imputation will be applied. FVIII activity after study discontinuation will be considered missing.

FVIII activity levels by visit will be summarized. In addition, the percentage of participants with FVIII activity level ≥ 40% will be reported by visit up to data cutoff.

3.2.6. Annualized FVIII Consumption

Annualized FVIII consumption will be reported by international unit (IU)/kg and total units (in IU), and a similar approach of data collection and endpoint derivation as described in Section 3.2.3 above for AIR will be used. FVIII consumption during the first 11 weeks will not be included.

3.2.7. Annualized Bleeding Rate of Specific Type

The ABR of specific type from Week 12 [Day 78] through at least 15 months (up to data cutoff) following PF-07055480 infusion as well as by yearly interval and by cumulative follow-up interval after the first 15 months will be reported separately by:

- Cause (spontaneous or traumatic)
- Location type (in all joints, in target joints, or in soft tissue)

Soft tissue includes soft tissue, muscle, and other (i.e., soft tissue/muscle/other). Per Protocol Appendix 7, a target joint is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period). A target joint is considered resolved when there are

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≤2 bleeds into the joint within a 12-month period. The investigator will assess the health of the target joint(s), identified at screening, as specified in the schedule of activities (SoA) of the protocol. Once a target joint is identified for a participant, the bleedings on this target joint will always be included in the ABR by target joint calculation even if the target joint is considered to have been resolved for any time period. The data collection and endpoint derivation are similar to what's described for Total ABR in Section 3.1.1.

3.2.8. Total ABR by Cause and by Location

Total ABR (treated and untreated) by cause and by location from Week 12 [Day 78] through at least 15 months (up to data cutoff) following PF-07055480 infusion is considered as a secondary endpoint. Total ABR by location will be also reported by yearly interval as well as by cumulative follow-up interval post PF-07055480 infusion. The data collection and endpoint derivation are similar to those described for Total ABR in Section 3.1.1 above.

3.2.9. Percentage of Participants without Bleeds

The percentage of participants without treated bleeds and the percentage of participants without treated and untreated bleeds will be reported for the observation period from Day 78 through data cutoff post PF-07055480 infusion, and by yearly interval (defined in Section 3.1.1) as well as by cumulative follow-up interval post PF-07055480 infusion as secondary endpoints. Data after resumption of prophylaxis or study discontinuation will be excluded from the summary. The percentage of participants without bleeds at baseline will be obtained from the lead-in study up to preinfusion of PF-07055480 and will also be reported for comparison.

3.2.10. Hemophilia Joint Health Score (HJHS)

Joint assessments will be performed using the HJHS version 2.1 to evaluate joint total (swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain, and strength) and global gait scores. HJHS data will be collected at Baseline, Week 24, Week 52, Week 104, Week 156, Week 208, and Week 260 or Early Discontinuation Visit. If the HJHS cannot be performed at Week 24 and/or Week 52, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit. Change in joint health score measured by the HJHS instrument will be summarized by visit.

Six joints (left ankle [LA], right ankle [RA], left elbow [LE], right elbow [RE], left knee [LK], right knee [RK]) will be scored on a scale from 0 to 20 according to the following criteria: duration of swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss, instability, joint pain, and strength. Gait will be scored on a scale from 0 to 4 based on walking, stairs, running, hopping on one leg. The total score will be the sum of scores from all 6 joints plus the gait score (range from 0 to 124). A higher total score will indicate more severe joint damage. The baseline assessment is based on the latest evaluation prior to PF-07055480 infusion, which is measured during the baseline period of this study.

The HJHS Total Score, ranging from 0 to 124, is obtained using the following formula:

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$$\text{HJHS Total Score} = \frac{\text{total score of evaluated items (excluding not evaluable items)}}{\text{possible maximum total score of evaluated items (excluding not evaluable items)}} \times 124$$

HJHS Total Score will not be derived if >20% of items are missing (including not evaluable [NE] items).

Note: there are 49 individual items to score, therefore 10 or more missing or NE will result in the total score not being calculated.

The derivation for the CSR reporting will be done ***solely based on 49 item scores***. That is, if investigator sites input any total score from work sheet, those 'calculated' inputs will NOT be used for derivation of the total score for the CSR reporting purpose.

3.2.11. Patient-Reported Outcome (PRO) Assessments

The PRO questionnaires should be completed (at Baseline, Week 12, Week 24, Week 52, Week 104, Week 156, Week 208 and Week 260 or early discontinuation visit) in accordance with the SoA during the scheduled site visits using a tablet device that will be provided to each site (or to the home-health vendor as applicable). Every effort should be made to conduct the PROs according to the protocol specified timepoints; however, if not feasible, baseline PROs have to be conducted any time prior to start of infusion on Day 1, postinfusion PROs at the next subsequent on-site visit or unplanned visit. At each relevant visit, the assessment questionnaires should be administered before dosing, treatment, or conversation between health care team and participants about their health condition. Participants should complete the questionnaires in a quiet area within the clinic (i.e., cannot be taken home) or at home (provided by the home-health vendor) and without help or interaction from family members or other caregivers. Spouses, family members, visitors, or health care team members should not assist the participant in answering questionnaires.

3.2.11.1. Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)

The Haem-A-QoL is a disease specific measure of health-related quality of life in patients with hemophilia. Intended for adults, the instrument uses a 4-week recall period to assess health across 10 domains consisting of 46 items. The 10 domains and the number of items within each domain of the adult version are the following: Physical Health (5 items); Feelings (4 items); View of Self (5 items); Sports and Leisure (5 items); Work and school (4 items); Dealing with Haemophilia (3 items); Treatment (8 items); Future (5 items); Family Planning (4 items); and Partnership and Sexuality (3 items). Scores are calculated by domain and a single total score. The 10 domains of health-related quality of life within each visit window will be summarized. Missing data will not be imputed to calculate the total score and score for an individual domain. Change from baseline in individual domain scores and the total score will be summarized by visit. The baseline assessment is based on the latest evaluation prior to PF-07055480 infusion, which is measured during the baseline period of this study.

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3.2.11.2. Hemophilia Activities List (HAL, Version 2)

The Hemophilia Activities List (version 2) is a multiple domain measure of the impact of hemophilia on functional abilities in adults. The 7 domains of this instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8 items); lower (leg) functioning (9 items); upper (arm) functioning (4 items); Transportation (3 items); Self-care (5 items); Household tasks (6 items); and Sports/Leisure (7 items). Scoring can be done by domain, components (Activities involving the Upper Extremities, Basic activities involving the Lower Extremities, and Complex activities involving the Lower Extremities) or a standardized total score.

All items are rated on a 6-point scale from 1 (impossible) to 6 (never) describing difficulty due to hemophilia in the past month. Several items allow the respondent to mark as 'not applicable'.

Selected items from five of the domains are used to create three components: upper extremity; basic lower extremity; and complex lower extremity activities.

Responses from individual items can be summed to give a score for each domain and component, and the total. Higher values indicate better quality of life, that is, higher values indicate less functional limitations in performing tasks.

The activities list also includes two sets of multiple-choice items assessing the use of adaptive and assistive devices; these items are not included in the scoring.

HAL baseline is the latest evaluation prior to PF-07055480 infusion, which is measured during the baseline preinfusion period of this study. The normalization method to derive score of domains and three components will be used to impute any missing item. Change from baseline in individual domain scores, component scores and the standardized total score will be summarized by visit.

3.3. Other Endpoints

3.3.1. Additional PRO Assessments

Additional PRO assessments implemented in this study are the HLIQ and the EQ-5D-5L. Additionally, 6 anchor items have been developed to assess change over time on the Haem-A-QoL, the HAL, and the HLIQ: three patient global impression of severity (PGIS) items and 3 patient global impression of change (PGIC) items. The 3 PGIS single item assessments will be completed at each clinic visit when the Haem-A-QoL, HAL and HLIQ are assessed. The 3 PGIC single item assessments will be also completed at each clinic visit when the Haem-A-QoL, HAL and HLIQ are assessed, but not at the baseline visit.

3.3.1.1. Hemophilia Life Impacts Questionnaire (HLIQ)

The HLIQ is a 9-item assessment of life impacts associated with living with and treating hemophilia. The HLIQ employs a 'past week' recall period. Four items are assessed on a 5-point, ordinal, verbal rating scale scored from 0 to 4, while 4 items are gated such that responding 'yes' branches to a 5-point, ordinal verbal rating scale and responding 'no' branches to a reason for not participating in the activity (i.e., due to hemophilia or due to

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other reasons). One item is assessed on a 4-point, ordinal, verbal rating scale scored from 0 to 3. Higher scores on the verbal rating scales indicate greater impact due to living with or treating hemophilia.

HLIQ baseline is the latest evaluation prior to PF-07055480 infusion, which is measured during the baseline period of this study.

3.3.1.2. Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

The PGIS-Physical Health (PH) is a single item assessment of the participant's overall impression of severity of physical health over the past 7 days. The response scale is a 4-point categorical rating scale ranging from 'none' to 'severe'.

The PGIS-Physical Functioning (PF) is a single item assessment of the participant's overall impression of severity of physical functioning over the past 7 days. The response scale is a 4-point categorical rating scale ranging from 'none' to 'severe'.

The PGIS-Hemophilia (H) is a single item assessment of the participant's overall impression of severity of life interference with hemophilia over the past 7 days. The response scale is a 4-point categorical rating scale ranging from 'none' to 'severe'.

The PGIC-PH is a single item assessment of the participant's overall impression of change in their physical health since receiving gene therapy. The response scale is a 5-point categorical rating centered around 'no change' with 2 grades of improvement and 2 grades of worsening.

The PGIC-PF is a single item assessment of the participant's overall impression of change in their physical functioning since receiving gene therapy. The response scale is a 5-point categorical rating centered around 'no change' with 2 grades of improvement and 2 grades of worsening.

The PGIC-H is a single item assessment of the participant's overall impression of change in their life with hemophilia since being enrolled in the study. The response scale is a 5-point categorical response scale centered around 'no change' with 2 grades of improvement and 2 grades of worsening.

Data for PGIC and PGIS endpoints will be summarized with counts (%) by response for each visit.

3.3.1.3. 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 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.

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The value of 5 dimensions at each visit will be reported. The visual analogue scale (VAS) score and the Index score will be compared with baseline and summarized by visit. Details of the Index score are provided in Section 6.3.1.3. Missing data will not be imputed, which means missing individual question responses will lead to missing dimension scores and total score. EQ-5D-5L baseline is the latest evaluation prior to PF-07055480 infusion, which is measured during the baseline period of this study.

3.3.2. Vector Shedding and Infectivity

Shedding will be assessed by quantitative real time polymerase chain reaction (PCR). Samples of plasma, saliva, PBMC, urine, and semen will be collected as specified in the SoA for analysis of vector shedding and infectivity. Peak values and the time to 3 consecutive specimens reaching the limit of quantification for each specimen type will be summarized.

Some participants (n=12), who consent to participate in an optional substudy, are expected to provide additional samples at early timepoints following study intervention (2 h [± 30 minutes], 24 h [± 3 h], 72 h [± 4 h] after completion of study intervention infusion and IV-line flush). This subset of samples will also be used for deoxyribonuclease (DNase) treatment for additional characterization. The data of this subgroup will be separately presented.

3.3.3. Pharmacodynamics

3.3.3.1. 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. Any sample taken within 72 hours after administering standard half-life exogenous FVIII replacement therapy, or 120 hours for products with extended half-life, for any purpose (including treatment of bleeding or prevention purposes), will be excluded from summary or analysis. In addition, FVIII antigen data will be excluded after participants have resumed prophylaxis regimen.

3.3.3.2. Von Willebrand Factor

Von Willebrand factor levels will be measured. This factor is the transport protein for FVIII, and its levels may influence FVIII levels and activity.

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

3.3.4. Joint Health Assessment

The following exploratory endpoints will be used to compare joint health post PF-07055480 infusion versus baseline:

- Number of target joints;
- Joint status as assessed by X-ray;
- Joint status as assessed by ultrasound.

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The definition of target joints is provided Section 3.2.7. Long-term joint outcomes will be based on the transition of participants to a mild hemophilia phenotype with maintenance of FVIII activity above the threshold to prevent joint bleeds supported by evidence of reduced target joint damage based on HJHS score and Pettersson score.

3.3.4.1. Ultrasound to Evaluate Joints

An ultrasound substudy will include a subset of participants (n~20) to undergo ultrasound exams to assess damage within joints by evaluating soft-tissue changes and osteochondral changes. The ultrasound scanning protocol will include data acquisition for both left and right sides of knees, elbows and ankles using the procedure and scoring method named Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US). Ultrasound scans will be acquired locally according to the SoA (i.e., at Screening or not later than Week4/Visit 6, Week 24, Week 52, or Early Discontinuation Visit) of the protocol.

HEAD-US is an additive scale for assessing severity of hypertrophic synovium and disease damage (in cartilage and bone separately) for each of the six joints. In addition, effusion (yes/no) will be recorded but not included in the score calculation.

3.3.4.2. X-ray Assessments to Evaluate Joints

Some participants (except for those participating in Germany) who consent to participate in an optional substudy, will undergo X-ray assessment for both left and right sides of knees, elbows, and ankles to assess damage within joints as detectable at a radiologic level. X-rays will be acquired according to the SoA (at Screening or not later than Week 4/Visit 6, Week 156, and Week 260 or Early Discontinuation Visit) of the protocol. All details of the X-ray acquisition will be captured in a separate scanning guide. At a minimum, joint images will be reviewed following the Pettersson scale. Central reading of X-ray images will be performed.

3.3.5. Effects on Coagulation

To evaluate for any effects on coagulation, the following assessments will be performed:

- Coagulation activation tests: aPTT, INR, D-dimer, TGA, TAT.
- Comparison of FVIII activity between one stage assay and chromogenic assay.
- Recovery of FVIII products post gene therapy.

3.3.6. Other Tertiary/Exploratory Endpoints

- Cellular immunity by cell-mediated assays.
- Binding IgG versus IgM assay.
- Other biomarkers as inflammatory cytokines.
- nAbs against other AAV serotypes.

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- Endpoints in the optional liver biopsy substudy [including vector integration in the liver, histopathology assessment (e.g., presence of fibrosis assessment, presence of lymphocytic invasion), protein and/or RNA expression of FVIII and selected biomarkers (e.g., Grp78, Gal3BP)].

3.4. Baseline Variables

A baseline for each relevant endpoint is defined in the above corresponding section, as needed.

3.5. Safety Endpoints

The safety endpoints of this study include vital signs, AEs, serious AEs (SAEs), physical examinations, electrocardiograms (ECG), liver ultrasounds, immunogenicity, and laboratory tests.

3.5.1. Adverse Events

The definitions of an AE or SAE can be found in Protocol Appendix 3.

All ongoing AEs and SAEs in the lead-in study (C0371004), including events of special interest, as defined in the lead-in study (C0371004), will be collected as medical history for this study. Historical data on Medical, Surgical and Hemophilia History will be captured from the lead-in study. Any new AEs/SAEs after completion of the lead-in study will follow the AE reporting process (in Protocol Appendix 3).

The time period for actively eliciting and collecting AEs and SAEs ('active collection period') for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (i.e., before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 5 years after the administration of the investigational product, or at End of Study (EOS) for participants who discontinue. The active collecting period for this study is categorized into short-term or long-term monitoring period and is defined later in this section.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the medical history/current medical conditions section of the case report form (CRF) not the AE section.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

During the short-term monitoring period (up to and including 104 weeks postinfusion) all SAEs (including medically important events, described in Protocol Appendix 3) and AEs will be collected.

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During the long-term monitoring period (Week 105 postinfusion to EOS) the following AEs will be collected:

- SAEs (including medically important events, Protocol Appendix 3).
- Nonserious AEs determined to be related to study intervention by the investigator or where causality is unknown.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

There is no lag time specified for reporting adverse events in this study. Treatment emergent adverse events (TEAEs) include any adverse events that occur on or after the start date of infusion of PF-07055480. TEAEs and SAEs will be summarized using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) for the follow-up through data cutoff, the short-term monitoring period (up to and including 104 weeks postinfusion), and the long-term monitoring period (Week 105 postinfusion to EOS) separately.

3.5.2. Laboratory Data

Data from protocol-required safety laboratory assessments will be summarized by visit. These laboratory tests are provided in Protocol Appendix 2.

3.5.3. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. Abnormal findings in physical examination will be summarized by MedDRA Preferred Term.

3.5.4. Vital Signs

Temperature (°C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic) will be assessed after at least 5 minutes rest in supine or upright position.

3.5.5. Cardiac Monitoring

- Local single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS and corrected QT intervals (QTc).
- Troponin I.

3.5.6. Liver Ultrasound

Liver surveillance by ultrasound (including hepatocellular carcinoma [HCC] detection) is planned as detailed in the SoA of the protocol.

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3.5.7. Immunogenicity

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

- Analysis of Anti-PF-07055480 Antibodies and Neutralizing Anti PF-07055480 Antibodies.
- Analysis of FVIII Inhibitor; if there are two FVIII inhibitor results (one from assay with DOAC reversal agent and one without) at the same visit, the result with DOAC reversal agent should be used.
- Analysis of Cellular Immune Response against AAV6 capsid and transgene by Enzyme-Linked Immune-Spot (ELISPOT).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following populations are defined:

Population	Description	Applicable Analysis (for additional information refer to Section 6)
Enrolled	All participants who sign the informed consent form (ICF) and meet all inclusion/exclusion criteria.	Disposition events summary
Dosed/Safety	All participants enrolled in the study and who receive the study intervention.	Demographic and baseline characteristics, hemophilia history, medical history, safety, nAbs, ADA, FVIII antigen, von Willebrand factor, vector shedding assessments, joint health assessments, efficacy sensitivity/supplementary analyses, PRO analyses, and coagulation activation tests.
Evaluable	All participants enrolled in the study and who receive the study intervention and have no significant interruption of efficacy measurement. The 'Evaluable' analysis population will include participants who receive the study intervention (full dose of infusion) and exclude participants with significant interruption of efficacy measurement. The significant interruption would occur if the participant discontinues from the study, is lost to follow-up, has significant	Efficacy sensitivity/supplementary analyses

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Population	Description	Applicable Analysis (for additional information refer to Section 6)
	interruption in data collection, or has a major protocol deviation.	
Efficacy	All participants in the 'Dosed' population who have completed at least 6 months of follow up in the lead-in study and at least 15 months of follow up or discontinued from the study C3731003 prior to the data cutoff for reporting.	Main analysis population for efficacy
Ultrasound Substudy	All participants who sign the additional ICF for the ultrasound substudy and meet all inclusion/exclusion criteria, and the participant's joint ultrasound have been reviewed following the extended ultrasound scale at baseline, and any data post-baseline.	HEAD-US ultrasound scale - total score and subscores, demographic and baseline characteristics, AEs, disposition, and FVIII activity level data.
Vector Shedding Substudy	All participants who sign the additional ICF for the Vector Shedding substudy and meet all inclusion/exclusion criteria, and who provide any additional vector shedding data for analysis.	Shedding vector levels in PBMC, saliva, urine, semen, and plasma; demographic and baseline characteristics, AEs, disposition, and FVIII activity level data.
Joint X-Ray Substudy	All participants who sign the additional ICF for the optional joint x-ray substudy.	Joint status as assessed by X-ray in Pettersson scale.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis will be conducted when at least 50 dosed participants have completed at least 15 months of follow up post PF-07055480 infusion. The primary analysis is focused on the efficacy and safety during the follow-up through data cutoff postinfusion. The associated efficacy endpoints and analysis methods are listed in the tables below. The final analysis will be conducted when all dosed participants have completed the entire study (i.e., 5 years in follow-up duration per participant) or discontinued prematurely from the study. The planned endpoints after the primary analysis are focused on extended efficacy and longer-term safety. As this is an open-label study, the sponsor may conduct reviews of the data during the course of the study for the purpose of safety assessments. There may be several periodic reviews of data between the primary analysis and the final analysis for the purpose of publications and regulatory updates, etc.

Category of Endpoint	Primary Analysis Endpoints And Statistical Analysis Methods
Primary	Total ABR (treated and untreated bleedings) from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be compared to preinfusion

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Category of Endpoint	Primary Analysis Endpoints And Statistical Analysis Methods
	of PF-07055480 (under SOC FVIII prophylaxis replacement regimen). A repeated measures negative binomial regression model will be used to test NI with NI margin = 3 bleeds/year at the one-sided alpha level = 0.025. If noninferiority is demonstrated, further testing for superiority would be conducted.
Key secondary	• FVIII activity level > 5% at 15 months postinfusion of PF-07055480. The percentage of participants will be compared to a null hypothesis of percentage ≤68% using an exact binomial test at the one-sided alpha level = 0.025. Based on the interim data of the Phase 1b/2 Study, 80% of participants in Cohort 4 (Phase 3 study dose) had a FVIII activity level greater than 5% at 18 months postinfusion. The null hypothesis of percentage ≤ 68% will be rejected if the observed percentage is greater than 80%. • Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF07055480 infusion will be analyzed separately using the same method as applied to Total ABR.
Secondary	The following secondary endpoints will be analyzed with one-sided test at the alpha level = 0.025 (except for the paired t-test with 2-sided alpha = 0.05) if listed in Table 8 for the gatekeeping process or summarized. • FVIII activity level from Week 12 through 15 months (up to Week 67) postinfusion of PF-07055480 will be summarized with descriptive statistics. • FVIII activity level will be summarized with descriptive statistics by visit. The number (%) of participants achieving specific FVIII activity thresholds (e.g., <1%, 1-5%, >5-<15%, 15-<40%, 40-≤150%, >150%) at selected visits postinfusion will be reported. • AIR (from Week 12 [Day 78] through at least 15 months [up to data cutoff] postinfusion of PF-07055480) will be compared to preinfusion of PF-07055480 (under SOC FVIII prophylaxis replacement regimen) using a paired t-test. • Annualized FVIII consumption from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be compared to preinfusion of PF-07055480 (under SOC FVIII prophylaxis replacement regimen) using a paired t-test. • Treated ABR by cause (spontaneous or traumatic) from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion of PF07055480 will be analyzed separately using the same method as applied to Total ABR. • Treated ABR by location (in joints, in target joints, or in soft tissue) from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be analyzed using the same method as applied to Total ABR. • Total ABR (treated and untreated) by cause and by location from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be analyzed using the same method as applied to Total ABR. • The percentage of participants without bleeds (from Week 12 [Day 78] through at least 15 months [up to data cutoff] postinfusion of PF-07055480) will be summarized. • HJHS by visit postinfusion of PF-07055480 will be compared to baseline using a paired t-test. • PRO endpoints (Haem-A-Qol, HAL) by visit postinfusion of PF07055480 will be summarized and compared to baseline to assess the improvement from baseline if baseline is available.

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Category of Endpoint	Primary Analysis Endpoints And Statistical Analysis Methods
Exploratory	Details are provided in later sections in this SAP.

Category of Endpoint	Primary Analysis / Final analysis Endpoints And Statistical Analysis Methods
Secondary (all final analysis endpoints are considered secondary in this study)	Analyses will be performed by yearly interval (Month 15, Years 2 through 5). Selected endpoints (as described in Section 6) will be also analyzed by cumulative follow-up interval.
Exploratory	Details of analyses for FVIII activity assays and other exploratory endpoints are described in later sections.

Category of Endpoint	Ultrasound Substudy
Exploratory	Joint images will be reviewed following the extended ultrasound scale with a final score combining soft tissue and osteochondral subscores and compared to screening (at Week 24 and Week 52 or EOS).

Category of Endpoint	Vector Shedding Substudy
Exploratory	A subset of participants (N=12) will have more extensive vector shedding analysis performed to further characterize the kinetics of vector shedding.

Category of Endpoint	Joint X-Ray Substudy
Exploratory	X-ray assessments will be performed to assess damage within joints as detectable at a radiologic level. X-rays will be acquired at Screening or not later than Week 4/Visit 6, Week 156, and Week 260 or Early Discontinuation Visit.

5.1. Hypotheses and Decision Rules

In this study, all hypothesis testing will be one-sided with Type I error of 0.025.

The primary objective is to evaluate the efficacy of a single infusion of PF-07055480 in participants ≥18 and <65 years of age with moderately severe to severe hemophilia A (FVIII:C ≤ 1%).

For the primary efficacy analysis, the hypothesis testing written in statistical notation is:

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H_0: Total ABR $_{PF-07055480}$ − Total ABR $_{FVIII\ prophylaxis}$ ≥3.0 versus H_a: Total ABR $_{PF-07055480}$ − Total ABR $_{FVIII\ prophylaxis}$ <3.0

where Total ABR $_{PF-07055480}$ represents the mean Total ABR post PF-07055480 infusion, while Total ABR $_{FVIII\ prophylaxis}$ represents the mean Total ABR on prior routine prophylaxis FVIII replacement. The proposed non-inferiority margin is 3.0 bleeds/year.

If the upper bound of the confidence interval of the difference (Total ABR $_{PF-07055480}$ − Total ABR $_{FVIII\ prophylaxis}$) is less than 3.0, the noninferiority would be demonstrated.

For the key secondary endpoint (FVIII activity level > 5%), the percentage of participants with FVIII activity level at 15 months post PF-07055480 infusion will be compared to the null hypothesis of percentage ≤ 68% using an exact test for binomial proportion. The other key secondary endpoint (Treated ABR) will be tested for noninferority using the same method and margin as described above for the Total ABR.

A gatekeeping process will be applied to control for multiple endpoint comparisons at the primary analysis. The subsequent hypothesis testing will only be performed after success on the previous hypothesis test. The testing ceases when a failure occurs. The sequence of gatekeeping process is displayed in Table 8 below. Note that only selected endpoints are included in the sequence.

Table 8. Gatekeeping Sequence

Order in the testing sequence	Statistical testing
1	Non-inferiority in Total ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment with a NI margin of 3
2	Percentage of participants with FVIII activity >5% at 15 months postinfusion compared to the null hypothesis of percentage ≤68%
3	NI in Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment with a NI margin of 3
4	Superiority in AIR from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment
5	Superiority in Annualized FVIII consumption (IU/kg) from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment
6	Superiority in Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment
7	Superiority in Total ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) postinfusion compared to prior prophylaxis treatment

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8	Haem-A-QoL Physical Health domain score significantly improved from baseline at 12 months postinfusion
9	HAL Complex Lower Extremity Activities domain score significantly improved from baseline at 12 months postinfusion

5.2. General Methods

Most safety evaluations are obtained via comparison of participants' baseline with data collected post PF-07055480 infusion in this study. Baseline is defined as the most recent observation collected prior to PF-07055480 infusion.

Efficacy assessments that compare experiences before and after PF-07055480 infusion will use data collected from the lead-in study C0371004 and preinfusion of PF-07055480 in C3731003 (while participants are on a regular FVIII prophylaxis regimen). FVIII activity is assessed by visit. Analysis details provided in Section 6 are for the primary analysis unless specified.

5.2.1. 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 percentage. The two-sided 95% confidence interval (CI) of the observed percentage will be provided (when appropriate) using the exact binomial method.

5.2.2. Analyses for Continuous Endpoints

The n, mean, median, standard deviation, Q1, Q3, minimum (min), maximum (max), and 95% CI of mean (when appropriate) for the observed value and the change from baseline by visit will be provided in the summary tables.

5.2.3. Analyses for Categorical Endpoints

In general, counts and percentages will be presented for categorical variables.

5.3. Methods to Manage Missing Data

In general, missing data will not be imputed in this study, unless specified in Section 3 and Section 6, where individual endpoints are discussed.

6. ANALYSES AND SUMMARIES

This section describes analysis details for the primary analysis.

6.1. Primary Endpoint

6.1.1. Total Annualized Bleeding Rate

6.1.1.1. Main Analysis

Total ABR will be analyzed using a repeated measures generalized linear model with negative binomial distribution, identity link function and generalized estimating equation (GEE) model form to account for within-participant correlation. Number of bleeds within

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the given follow-up period will be the dependent variable in the model. 'Year' and an interaction of year by treatment (treatment of prophylaxis or PF-07055480) will be included in the model. 'Year' is a numeric measure of time in the unit of year in the given follow-up period. 'Treatment' will be a class factor in the model, and 'subject' (i.e., participant) will be a random effect. No other covariates will be included in the model. Detailed specification for the model and parameters is provided in Appendix 1.1.

- The 'Efficacy' population will be the main analysis population for the primary analysis.

- The Total ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF-07055480 infusion will be compared to participants' Total ABR on prior FVIII prophylaxis regimen before infusion. The estimation of difference and CI will be constructed. If the upper bound of the confidence interval of the difference of (Total ABR $_{\text{PF-07055480}}$ – Total ABR $_{\text{FVIII prophylaxis}}$) is less than 3.0, then statistical significance of the noninferiority would be demonstrated. An example of SAS code of such analysis is included in Appendix 1.2. If noninferiority is demonstrated, further testing for superiority would be conducted, using the same method, except the margin would be set to 0.

The summary table will include two columns, for FVIII prophylaxis (pre-PF-07055480) and PF-07055480 (post-PF-07055480), respectively. The descriptive statistics including n, mean, standard deviation, median, Q1, Q3, min, max of the observed Total ABR, estimated means with 95% CI of estimated means (model derived), estimated difference in mean Total ABRs (model derived), one-sided p-value, and the 95% CI of the difference in mean Total ABRs (model derived) will be presented in the summary table. In addition, percent reduction in mean Total ABR, one-sided p-value, and the corresponding 95% CI will be estimated from a separate analysis model with log link function. An example of SAS code for this analysis model is provided in Appendix 1.3.

6.1.1.2. Sensitivity/Supplementary Analyses

The following sensitivity analyses will be performed for Total ABR in the primary analysis without hypothesis testing unless specified:

- The same analysis model and summary as described above for the main analysis will be repeated on the Total ABR from Week 12 through data cutoff, using the 'Dosed' population regardless of the length of follow-up in preinfusion or postinfusion.

- Same analysis as described for the main analysis will be performed on the Total ABR from Week 12 through data cutoff, using the 'Evaluable' population if it is different from the 'Dosed' population.

- Two sensitivity analyses will be performed to include the bleeding data collected during only the latest 6 months and the first 6 months separately during the lead-in study up to preinfusion of PF-07055480 in order to support the robustness of the primary analysis results and confirm the absence of seasonal effect, using the

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'Efficacy' population. In these sensitivity analyses, all the participants will have the same length (i.e., 6 months) of preinfusion observation period.

- Include only the data collected in the lead-in study (C0371004) (i.e., excluding the preinfusion data in C3731003) and the data postinfusion of PF-07055480 using the same analysis model as described above. This analysis will be conducted on the 'Efficacy' population.

Additional US-specific analyses are described in Appendix 1.4.

Supplementary analyses (to be conducted on the 'Efficacy' population): Total ABR 15 months, Year 2, Year 3, Year 4, and Year 5 as defined in Section 3.1.1, as well as Total ABR in cumulative follow-up intervals (i.e., from Week 12 [Day 78] through 2 years postinfusion, from Week 12 [Day 78] through 3 years postinfusion, etc.), will be compared separately to Total ABR of FVIII prophylaxis (pre-PF-07055480) using the same statistical method as for Total ABR as described in Section 6.1.1.1 except that noninferiority test or superiority test won't be performed. For analyses by yearly interval, participants who have discontinued from the study or resumed prophylaxis regimen prior to the start of a given yearly interval will be excluded.

The descriptive statistics including n, mean, standard deviation, median, Q1, Q3, min, max of the observed Total ABR, estimated means with 95% CI of estimated means (model derived), estimated difference in mean Total ABRs (model derived), and the 95% CI of the difference in mean Total ABRs (model derived) will be presented in the summary table.

6.1.1.3. Assessment of Treatment Failure

At Regulatory Agency's request, a participant-level listing including the following variables will be provided for the 'Dosed' population to identify participants with treatment failure:

(1) Participant's Subject ID
(2) Visit number (indicating scheduled or unscheduled)
(3) Study Day relative to infusion day
(4) Unconfounded FVIII activity by chromogenic assay
(5) Description of the bleed (e.g., traumatic or spontaneous) if a bleed occurred
(6) Reason for use of FVIII infusion if an FVIII infusion was used
(7) Study Day of prophylaxis resumption
(8) Reason of prophylaxis resumption

Unconfounded FVIII activity data are the appropriate FVIII activity data that are collected beyond 72 hours after administering FVIII infusion with standard half-life or 120 hours with extended half-life. This data listing will include a row when there is an occurrence in any of the variables in (4), (5), (6) and (7). The last row for each participant will include the Study Day on data cutoff for the given participant. Clinical review will be conducted using this listing to identify participants with treatment failure.

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6.2. Secondary Endpoints

6.2.1. Key Secondary Endpoint: FVIII Activity Level > 5%

6.2.1.1. Main Analysis

The percentage of participants with FVIII activity level > 5% at 15 months postinfusion will be tested against the null hypothesis of percentage ≤ 68% using a one-sided exact binomial proportion test at one-sided alpha = 0.025 using the 'Efficacy' population. The number of participants in the analysis population, number of participants with FVIII activity level > 5%, percentage with the 95% CI of the percentage, and p-value will be provided.

Participants who prematurely discontinue from the study or resume prophylaxis regimen prior to reaching Month 15 visit will be considered as having FVIII activity ≤ 5% for this percentage assessment.

The 15 months postinfusion is corresponding to a study visit at Week 65. Any appropriate FVIII activity data collected at unscheduled visits during Week 63 to Week 67 (i.e., the visit window for Week 65 visit) will be included in this assessment. Imputation rules as described in Section 3.2.1 will be applied.

6.2.1.2. Sensitivity/Supplementary Analysis

The number (%) of participants achieving specific FVIII activity intervals via CA and OS assays separately (e.g., <1%, 1-5%, >5-<15%, 15-<40%, 40-≤150%, >150%) at Week 12, Week 26 (Month 6), Week 52 (Month 12), Month 15, Month 18, Year 2, Year 3, Year 4, and Year 5 postinfusion will be summarized separately for the 'Dosed' population. For visualization, a stacked bar chart will be generated, presenting percentage of participants achieving specific FVIII activity thresholds via CA and OS assays mentioned above at the given time points based on the 'Dosed' population.

The number of participants present at the beginning of each protocol-defined visit window will be used as the denominator for percentage calculation. Imputation rules as described in Section 3.2.5 will be applied.

6.2.2. Key Secondary Endpoint: Treated ABR

6.2.2.1. Main Analysis

Treated ABR from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF-07055480 infusion will be analyzed using the same main analysis method as for Total ABR on the 'Efficacy' population.

6.2.2.2. Sensitivity/Supplementary Analysis

The following sensitivity analyses will be conducted:

- For completeness, the same analysis model and summary used for the main analysis will be repeated for the Treated ABR from Week 12 through data cutoff, using the 'Dosed' population (regardless of the length of follow-up in preinfusion or postinfusion).

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- Same analysis as described for the main analysis will be performed on the Treated ABR from Week 12 through data cutoff, using the 'Evaluable' population if it is different from the 'Dosed' population.

As supplementary analyses, Treated ABR by yearly interval and by cumulative follow-up interval post PF-07055480 infusion are considered as secondary endpoints and will be analyzed using the same analysis model and summary as for the main analysis of Total ABR (using the 'Efficacy' population).

No other sensitivity/supplementary analyses will be conducted.

6.2.3. AIR of Exogenous FVIII

6.2.3.1. Main Analysis

AIR of exogenous FVIII from Week 12 [Day 78] through at least 15 months (up to data cutoff) post PF-07055480 infusion vs AIR during FVIII prophylaxis replacement regimen will be tested with a paired t-test for superiority to demonstrate the reduction of overall burden in the participants.

- The 'Efficacy' population will be the main analysis population for the primary analysis.

- The summary table will include two columns, for FVIII prophylaxis (pre PF-07055480) and PF-07055480 (post PF-07055480), respectively. The descriptive statistics including number of participants (n), mean, median, Q1, Q3, min, max of the observed AIR, mean difference of (AIR PF-07055480 – AIR FVIII prophylaxis), and the 95% CI of the mean difference will be presented in the summary table. In addition, the p-value from the paired t-test will be provided. The percent reduction in mean AIR will be derived as 100*[1– (mean AIR PF-07055480)/ (mean AIR FVIII prophylaxis)].

6.2.3.2. Sensitivity/Supplementary Analysis

The following sensitivity analyses will be conducted:

- The same analysis and summary as described above will be repeated for the AIR from Week 12 through data cutoff, using the 'Dosed' population (regardless of the length of follow-up preinfusion or postinfusion).

- To include only the data collected in the lead-in study (C0371004) (i.e., excluding the preinfusion data in C3731003) and the data postinfusion of PF-07055480 using the same analysis model as the main analysis. This analysis will be conducted on the 'Efficacy' population.

As supplementary analyses, AIR in yearly intervals, as well as AIR in cumulative follow-up intervals (i.e., from Week 12 through 2 years postinfusion, from Week 12 through 3 years postinfusion, etc.) as defined in Section 3.1.1, will be tested separately with the same method

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as for the main analysis using the 'Efficacy' population to demonstrate superiority over AIR of FVIII prophylaxis replacement regimen as secondary endpoints.

In addition, percentage of participants who have resumed prophylaxis regimen and descriptive statistics for the time to prophylaxis resumption will be reported for the above-mentioned time periods (i.e., from Week 12 through data cutoff, by yearly interval, and by cumulative follow-up interval) in the 'Efficacy' population and the 'Dosed' population separately.

6.2.4. FVIII Activity Level from Week 12 through 15 Months Postinfusion

The FVIII activity level will be calculated for each participant as a geometric mean of all eligible FVIII activity measures from Week 12 through 15 months post PF-07055480 infusion using the 'Efficacy' population. Imputation rules for FVIII activity as described in Section 3.2.4 will be applied. The number of participants (n), mean, standard deviation, median, Q1, Q3, min, max, and 95% CI of mean will be reported in the summary tables. No hypothesis testing will be performed for the geometric mean of FVIII activity level.

6.2.5. FVIII Activity Level by Visit

FVIII activity data in the 'Dosed' population will be summarized by visit up to data cutoff with descriptive statistics and 95% CI of mean. Imputation rules as described in Section 3.2.5 will be applied. Order statistics (consisting of minimum, percentiles at 10%, 25%, 50%, 75%, and 90%, and maximum) will be provided for FVIII activity data at Weeks 26, 52 (Month 12), 65 (Month 15), 104 (Year 2), and 156 (Year 3).

FVIII activity will be imputed with 0.9% through data cutoff after the participants have resumed prophylaxis regimen and after they discontinued from the study due to lack of efficacy. In addition, the number and percentage of participants with FVIII activity ≥ 40% will be reported by visit. No hypothesis testing will be performed.

A box-and-whisker plot with study week in the X-axis and FVIII activity level (% of normal) in the Y-axis will be provided for each assay method from central laboratory starting from Week 3 since prophylaxis treatment is allowed during the first 2 weeks postinfusion. The onset of FVIII activity steady state will be assessed by a visual inspection on the box-and-whisker plot for the FVIII activity data based on the central chromogenic assay.

The following supplementary plots (to include appropriate FVIII activity data that were collected beyond 72 hours after administering FVIII infusion with standard half-life or 120 hours with extended half-life products) will be generated for the 'Dosed' population.

- The FVIII activity (from central chromogenic assay) along with FVIII activity from one-stage assay (central, local) will be visualized in a scatter plot with chromogenic assay results on the x-axis and one-stage assay results (central and local separately) on the y-axis. Missing data (including discontinuation from the study) won't be imputed and data post prophylaxis resumption will be excluded. The Pearson's correlation will be calculated for each pair of the chromogenic vs one-stage assays.

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- An additional scatter plot of FVIII activity from central one-stage assay versus FVIII activity from local one-stage assay with central results on the x-axis and local results on the y-axis. Missing data (including discontinuation from the study) won't be imputed and data post prophylaxis resumption will be excluded. The Pearson's correlation will be calculated and provided.

- A spaghetti plot including all participant-level FVIII activity levels postinfusion for each assay method separately from central laboratory over time to data cutoff, including FVIII activity imputation rules described in Section 3.2.5.

- Individual plots presenting all FVIII activity data (initial and retested results) will be provided for the participants who had samples collected while using DOAC before implementing the further validated assays.

6.2.6. Annualized FVIII Consumption

This endpoint will be analyzed similarly as AIR, including main analysis, timing of the analysis, and table presentation.

One sensitivity analysis will be performed to include only the data collected in the lead-in study (C0371004) and the data postinfusion of PF-07055480 using the same analysis model as described above. This analysis will be conducted on the 'Efficacy' population.

In addition, the annualized FVIII consumption from Week 12 through data cutoff will be analyzed using the 'Dosed' population (regardless of the length of follow-up preinfusion or postinfusion).

As supplementary analyses, annualized FVIII consumption in yearly intervals, as well as in cumulative follow-up intervals (i.e., from Week 12 through 2 years postinfusion, from Week 12 through 3 years postinfusion, etc.) as defined in Section 3.1.1, will be tested separately using the same method as for the main analysis using the 'Efficacy' population to compare with the annualized FVIII consumption of FVIII prophylaxis replacement regimen as secondary endpoints.

6.2.7. Treated Annualized Bleeding Rate of Specific Type

This Treated ABR of specific type includes Treated ABR by:

- Cause (spontaneous or traumatic).
- Location type (in all joints, in target joints, or in soft tissue/muscle/other).

These endpoints will be analyzed using the same main analysis method as for Total ABR from Week 12 through at least 15 months (up to data cutoff) postinfusion and by yearly interval, as well as by cumulative follow-up interval post PF-07055480 infusion on the 'Efficacy' population. NI, superiority testing or sensitivity analyses will not be conducted for this endpoint. In addition, as a supplementary analysis, Treated ABR by cause within each location [i.e., (spontaneous, traumatic) x (joint, target joint, soft tissue/muscle/other)] from Week 12 through at least 15 months (up to data cutoff) post PF-07055480 infusion will

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be summarized with descriptive statistics (without comparison to lead-in data) on the 'Efficacy' population.

6.2.8. Total ABR (treated and untreated bleedings) by Cause and by Location

Total ABR by cause and by location will be analyzed separately using the same main analysis method as for Total ABR from Week 12 through at least 15 months (up to data cutoff) postinfusion and by yearly interval as well as by cumulative follow-up interval post PF-07055480 infusion on the 'Efficacy' population. NI, superiority testing or sensitivity analyses will not be conducted for this endpoint. In addition, as a supplementary analysis, Total ABR by cause within each location [i.e., (spontaneous, traumatic) x (joint, target joint, soft tissue/muscle/other)] from Week 12 through at least 15 months (up to data cutoff) post PF-07055480 infusion will be summarized with descriptive statistics (without comparison to lead-in data) on the 'Efficacy' population.

6.2.9. Percentage of Participants without Bleeds

Percentage of participants without treated bleeds will be reported for the same time periods as for Total ABR: from Week 12 through at least 15 months (up to data cutoff) post PF-07055480 infusion, by yearly interval as well as by cumulative follow-up interval. The yearly intervals and cumulative follow-up intervals are defined in Section 3.1.1.

The percentage of participants without treated and untreated bleeds will be reported for the same time periods as for Total ABR: from Week 12 through at least 15 months (up to data cutoff) post PF-07055480 infusion, by yearly interval as well as by cumulative follow-up interval.

The summary tables will be provided for the time periods mentioned above and will include the number of participants included in the specified time interval, frequencies, and the percentage of participants with or without bleeding. The 'Efficacy' population will be used for the summary.

In addition, the percentage of participants without treated and untreated bleeds from Week 12 through data cutoff post PF-07055480 infusion will be reported for the 'Dosed' population.

6.2.10. Hemophilia Joint Health Score (HJHS)

The HJHS total score at different time points will be compared to the baseline using a paired t-test.

The number of participants (n), mean, median, standard deviation, Q1, Q3, min, max, and the 95% CI of mean for the observed value and change from baseline, as well as the p-value from the paired t-test for change from baseline, will be presented by visit based on the 'Dosed' population.

6.2.11. PRO Assessments

Haem-A-QoL and HAL endpoints will be analyzed as continuous or categorical variables according to the data type. For each visit, the observed value post PF-07055480 infusion will be compared to the baseline using paired t-test for continuous variables.

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For the primary analysis, Haem-A-QoL Physical Health domain score and HAL Complex Lower Extremity Activities domain score at Month 12 are included in the gatekeeping sequence for hypothesis testing. To avoid missing data in the assessment at Month 12, HJHS/PRO data collected at unscheduled visits during Month 12 through Month 15 (i.e., during Week 51 through Week 65) will be included for Month 12 assessment.

6.2.11.1. Haem-A-QoL

The Haem-A-QoL assesses health-related quality of life (HRQoL) in adult patients >=17 years of age with haemophilia. It included 46 items contributing to 10 HRQoL domains, as depicted in the table below. All Haem-A-QoL items are based on a 5-point Likert-type scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often and 5 = all the time). A 'Not applicable' response option is also available for the domains of 'Sports and Leisure', 'Work and School', and 'Family Planning' when the question may not apply to the participant. Some of the items need to be re-coded.

The items prompt the responder to consider life in the last four weeks ('four-week recall'). Scoring is performed by averaging the non-missing item responses for each domain, and then rescaled to be on 0 to 100, with lower scores representing higher quality of life. The total score is directly averaged across the 46 items values and then rescaled on zero to 100.

The 10 domain scores of health-related quality of life as well as the total score will be assessed and compared to the corresponding baseline using paired t-test. The Physical Health domain is considered the main endpoint of this instrument. A domain score can be calculated if ≥ 50% of that domain's items have been answered.

The number of participants with non-missing observations (n), mean, median, standard deviation, Q1, Q3, min, max, and the 95% CI of mean for the observed value and change from baseline, as well as the p-value from the paired t-test for change from baseline, will be provided separately for domains and total score by visit based on the 'Dosed' population.

6.2.11.2. Hemophilia Activities List (HAL, v2)

The 7 domains of the activities HALs and three component scores can be calculated, and each will be compared to the corresponding baseline using a paired t-test. Each domain or component, or the total, has a required minimum number of valid responses or the score is set to missing. An implication of the 'minimum number of valid responses' is that there is an acceptable amount of missing data where the scores (domains, components, and total; raw and normalized) can still be calculated. Complex activities involving the Lower Extremities is considered as the main endpoint for this instrument.

The number of participants (n), mean, median, standard deviation, Q1, Q3, min, max, and the 95% CI of mean for the observed value after normalization and change from baseline, as well as the p-value from the paired t-test for change from baseline, will be provided by visit based on the 'Dosed' population.

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6.3. Other Endpoints

6.3.1. Additional PRO Assessments

6.3.1.1. Hemophilia Life Impacts Questionnaire (HLIQ)

The HLIQ is a 9-item assessment of life impacts associated with living with and treating hemophilia. These 9 individual item scores will be compared to the corresponding baseline using paired t-test.

The number of participants, counts and percent by response to individual items will be provided by visit based on the 'Dosed' population.

6.3.1.2. PGIS and PGIC

The PGIS-PH, PGIC-PH, PGIS-PF, PGIC-PF, PGIS-H and PGIC-H global items are collected to enable an anchor-based method for interpreting changes in the Haem-A-QoL (-PH), HAL (-PF) and HLIQ (-H), respectively. These interpretation analyses will be described in a separate analysis plan. The PRO interpretation results will be reported separately from the CSR.

For the CSR, data of PGIC and PGIS endpoints will be summarized with counts (%) by response for each visit based on the 'Dosed' population.

6.3.1.3. EQ-5D-5L

Each of the 5 dimensions (i.e., 'Mobility', 'Self-care', 'Usual activities', 'Pain/discomfort', and 'Anxiety/depression') in the EQ-5D 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 study CSR, weights under the United States population will be used to obtain the Index score.

Scores of the 5 dimensions will be summarized with counts and percent for scores in each

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dimension by visit.

The number of participants with non-missing observations (n), mean, median, standard deviation, Q1, Q3, min, max, and the 95% CI of mean for the observed value and change from baseline, as well as the p-value from the paired t-test for change from baseline, will be provided for the Index score and VAS score by visit based on the 'Dosed' population.

6.3.2. Vector Shedding and Infectivity

Descriptive summaries of shedding vector levels in PBMC, saliva, urine, semen, and plasma will be provided, including a summary of peak vector levels, time to peak vector levels and time to undetectable/negative vector. Vector levels that are reported as below the lower limit of quantification (<LLoQ) by the bioanalytical laboratory are considered as negative. A peak level is defined for each participant as the highest vector level collected prior to the first set of 3 consecutive negative results in a given specimen type. If multiple assessments are collected for a study visit, the highest value will be included in the summary as a conservative approach. Number and percentage of participants who achieved 3 consecutive negative results will be reported for each specimen. Number and percentage of participants <LLoQ at each visit will also be summarized in the table.

The following time to event endpoints will be derived using the first set of three consecutive negative results in a given specimen type. Time to undetectable/negative vector (defined as time to first of three consecutive negative results), time to last of three consecutive negative results, and time to the last positive prior to three consecutive negatives will be summarized. The number of participants (n), mean, median, standard deviation, Q1, Q3, min, and max will be presented by visit in summary tables. A median plot of vector shedding over time will be generated with specimen types differentiated by different color/symbols. A box and whisker plot of vector levels over time will be generated for each specimen.

The summary table will be generated for the 'Vector Shedding Substudy' population (described in Section 3.3.2) and the 'Dosed' population. 'Vector Shedding' subgroup (optional substudy) will have more extensive vector shedding analysis performed on their specimens to further characterize the kinetics of vector shedding. The data of this subgroup will be separately presented.

Samples from the substudy will also be assessed by DNase digestion method for saliva, semen, and urine. Results from both DNase digested and undigested samples will be summarized separately in another table. Individual plots of vector shedding over time will be generated for all subjects and the figures will be presented in log-linear scales. In the individual plots, <LLoQ values will be imputed as one half of the LLoQ value for plotting purposes. The plot will be paged by participant and paneled by specimen type, and results from both lab methods will be plotted on the same figure, differentiated by color/symbols. Results from the two methods will be presented side by side in a data listing.

In addition, baseline, demographic characteristics, weight, body mass index, and FVIII activity level data collected for the participants in this substudy will be summarized.

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6.3.3. Pharmacodynamics: FVIII antigen levels and von Willebrand factor

The number of participants (n), mean, median, standard deviation, Q1, Q3, min and max by study visit will be provided in the summary tables for FVIII antigen levels and for von Willebrand factor as specified in Section 3.3.3.

6.3.4. Joint Health Assessments

6.3.4.1. Target Joints

Assessment for target joints (hip, elbow, wrist, shoulder, knee, and ankle) will be performed at Screening as part of hemophilia history. A target joint is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (3 or more spontaneous bleeds into a single joint within a consecutive 6-month period). A target joint is considered resolved when there are ≤2 bleeds into the joint within a 12-month period.

Number and percentage of participants with 0, 1, 2 or ≥3 target joints at baseline, during the first 15 months post PF-07055480 infusion, and by cumulative follow-up intervals will be summarized, respectively. Number and percentage of participants who have 0, 1, 2 or ≥3 baseline target joints resolved during the first 15 months post PF-07055480 infusion, and by cumulative follow-up interval will be summarized. Similarly, number and percentage of participants who developed new target joints (1, 2 or ≥3 target joints) during the first 15 months post PF-07055480 infusion, and by cumulative follow-up interval will be summarized. The number and location of target joints at baseline and post PF-07055480 infusion will be provided in a data listing. The summary will be based on the 'Dosed' population.

6.3.4.2. X-ray Assessments to Evaluate Joints

Total score, scores at specific joints, and scores at target joints based on the Pettersson scale, as well as the change from baseline will be summarized. The observed values will be compared to the corresponding baseline using paired t-test.

The number of participants with non-missing observations (n), mean, median, standard deviation, Q1, Q3, min, max, and the 95% CI of mean for the observed value and change from baseline, as well as the p-value from the paired t-test for change from baseline, will be provided by visit based on the 'Joint X-Ray Substudy' population.

6.3.4.3. Ultrasound Substudy

A subset of participants (n~20) will undergo ultrasound exams (at Screening, Week 24, and Week 52) to assess damage within joints by evaluating soft-tissue changes and osteochondral changes. The ultrasound scanning protocol will include acquisition of knees, elbows, and ankles.

Joint images will be reviewed following the extended ultrasound scale (i.e., HEAD-US) with a final score combining soft tissue and osteochondral subscores and compared to baseline (at Screening period). Total score for each joint will be summarized by visit with descriptive statistics and 95% CI for mean observed value and mean change from baseline.

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In addition, demographic and baseline characteristics, AEs, disposition, and FVIII activity level data collected for the participants in this substudy will be summarized.

Summary tables will be generated for the participants in 'Evaluable' population in the 'Ultrasound Substudy' population.

6.3.5. Optional Liver Biopsy Substudy

One optional liver biopsy can be performed (in participants who consent to do so and as per investigator's judgement) during Year 1 postinfusion and/or subsequently during Years 2-5 postinfusion. 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 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.

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

Demographic information, baseline characteristics of 'Dosed' population will be summarized. Medical history/Hemophilia history data at study entry, including information collected in the lead-in study (C0371004) will also be summarized.

In addition, demographic and baseline characteristics will be summarized separately for the main analysis population (i.e., 'Efficacy' population).

6.5.2. Study Conduct and Participant Disposition

The participants' disposition will be summarized.

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6.5.3. Study Treatment Exposure

Since there is only one dose of the study medicine, there is no plan to measure treatment exposure or compliance in this study. Instead, the percentage of participants with partial dose of PF-07055480 infusion will be reported.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant medication other than FVIII replacement infusions, which will be summarized separately as a secondary endpoint, and non-drug treatment will be summarized.

The following data will be summarized to assess corticosteroid treatment:

- Participants (%) with corticosteroid treatment.
- Participants (%) with corticosteroid dose escalation during corticosteroid treatment. In addition, number (%) of participants by number of dose escalations will be reported.
- Time to corticosteroid initiation: to be calculated as [date of first corticosteroid initiation – giroctocogene fitelparvovec infusion date +1].
- Total time on corticosteroids: to be calculated as [stop date of last dose of corticosteroid – date of initiation of first dose of corticosteroid +1] excluding days without corticosteroid use during the period from first corticosteroid initiation until the last dose of corticosteroid.
- The entire duration from corticosteroid initiation through the last administration: to be calculated as [last date of corticosteroid treatment – first date of corticosteroid initiation + 1].
- Duration of follow-up (in days) post cessation of the latest corticosteroid therapy in the participants who received corticosteroid: to be calculated as [data cut-off date or discontinuation date (whichever comes earlier) – stop date from the last dose of corticosteroid]. Days of follow-up duration will be converted to months.
- Cumulative prednisone-equivalent dose. Both dose and frequency will be included for the calculation of cumulative dose. Doses of different corticosteroid concomitant medications will be converted to prednisone-equivalent dose using the following conversion table. For example, one dose of triamcinolone is equal to 5/4=1.25 prednisone-equivalent dose. The prednisone-equivalent dose for budesonide is 5/1.125=4.44.

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Glucocorticoids	Equivalent dose (mg)
Short-acting	
Cortisol	20
Cortisone	25
Intermediate-acting	
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Budesonide	1.125
Long-acting	
Dexamethasone	0.75
Betamethasone	0.6
Mineralocorticoids	
Fludrocortisone	2
Sources provided in Section 8.	

- Average daily prednisone-equivalent dose per participant.
- Number of corticosteroid courses per participant. A corticosteroid course will be defined below per participant and used to calculate number of CS (corticosteroid) courses: The start date of a CS course will be defined as the time of the first dose of CS or when a dose increase was made. The end date will be defined as the day before CS use was discontinued, or the day before a dose increase was made.

FVIII replacement infusion post PF-07055480 infusion will be reported in a separate data listing in addition to summary tables as described in Section 6.2.3 and Section 6.2.6.

6.6. Safety Summaries and Analyses

All safety analyses, including analyses of AEs, clinical laboratory results, vital signs, and physical examinations will be conducted on the 'Safety' analysis population. In this study, 'Safety' population is the same as 'Dosed' population.

6.6.1. Adverse Events

The AE data will be summarized following the latest available version of MedDRA.

An overall table summarizing TEAEs reported during the entire study will be sorted by System Organ Class (SOC) and Preferred Term (PT). Per protocol, adverse events assessed as non-serious and unrelated to study drug are reported within the first two years postinfusion only and are not subject to reporting thereafter. Therefore, the all causality TEAE tables will include a footnote to convey non-serious unrelated AEs were collected over the first two years and not the subsequent 3-year study duration for a given participant.

All TEAEs occurring during the short-term monitoring period (up to and including 104 weeks postinfusion) will be summarized, sorted by SOC and PT. All AE summary tables

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will be generated to display all AEs, relationship to study drug, and severity of the AEs ('Mild', 'Moderate', and 'Severe').

All serious AEs, treatment-related non-serious AEs, events of special interest, AEs related to corticosteroid treatment as deemed by the investigator, AEs leading to study discontinuation, and AEs leading to death will be summarized for adverse events reported during the short-term monitoring period (up to and including 104 weeks postinfusion) and AEs reported during the long-term monitoring (Week 105 post PF-07055480 infusion up to EOS), respectively if data are available.

TEAEs and SAEs will be summarized separately for the 'Safety' population.

6.6.2. Laboratory Data

Data of safety laboratory tests and other laboratory tests collected at scheduled study visits will be summarized according to the data type. Data collected at both scheduled visit and unscheduled visits will be included in plots.

Any important laboratory abnormality identified will be summarized as described below.

Categorical shift of abnormal to normal, or normal to abnormal, in liver function test (LFT), α-Fetoprotein (AFP), hematology, and clinical chemistry parameters will be summarized.

Laboratory tests included in LFT measures are listed in the Protocol Appendix 2. Baseline and post baseline observations will be summarized with descriptive statistics by visit and will be presented in a data listing. Number of participants (n), mean, SD, median, Q1, Q3, min and max will be presented for all change from baseline tables. Individual laboratory values will be classified according to whether the test result is 'low' (i.e., below the lower limit of normal), 'normal' (i.e., within the normal range), or 'high' (i.e., above the upper limit of normal). The abnormality categorical data will be summarized in shift tables comparing the results at the end of study visit, minimum post-baseline, and maximum post-baseline with those at the baseline visit.

The following laboratory tests presented in Table 9 will be reported in shift tables.

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Table 9. Laboratory Tests to be Presented in Shift Tables

Hemoglobin
Hematocrit
Selected LFTs, including albumin, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (total, direct), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactic acid dehydrogenase (LDH)
AFP
aPTT (in ratio), INR, TAT, TGA, D-dimer
White blood cell (WBC) count total
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Serum creatinine

An individual participant plot that presents ALT/AST, factor activity levels, ELISPOT data, corticosteroid use and dose, bleeding episodes and factor replacement infusions will be provided for each participant in the 'Safety' population. Three panels will be provided for each individual plot. In the top panel, FVIII activity (based on central chromogenic assay) and ALT/AST levels over time will be plotted, with all bleeds and exogenous FVIII infusions marked. ELISPOT data (selected parameters related to T-cell response to AAV capsid protein and FVIII) over time will be plotted underneath as a separate panel. The start/stop days of corticosteroid with corresponding doses will be plotted in the last panel.

In a case when a FVIII infusion has to be administered for a planned surgery or resumption of prophylaxis regimen, the FVIII activity data collected by local labs before FVIII infusion and 30 minutes post FVIII infusion will be used to calculate the recovery as [(FVIII activity post FVIII infusion – FVIII activity pre FVIII infusion)/dose of FVIII infusion]. This calculated recovery will be compared to the expected recovery in hemophilia A population, based on the number of units infused. A data listing will be provided with participant-level data of FVIII activity levels (pre and post FVIII infusion), dose of FVIII infusion, and calculated recovery.

6.6.3. Vital Signs/ Physical Examination/Other Safety Outcome

Vital signs by visit, electrocardiograms, liver ultrasounds, and abnormal findings from physical examination will be summarized according to the data type.

6.6.4. Immunogenicity

Percentage of participants with positive/negative interferon gamma (IFNγ) to each AAV or FVIII pool, FVIII overall and capsid overall, compare to baseline, will be summarized by the specified sampling timepoint for participants in whom the corticosteroid treatment is initiated.

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Descriptive summaries will be provided for nAb to AAV titer by study visit. Number and percentage of participants with positive nAb to AAV will be summarized by study visit. Unscheduled assessments will also be presented. Data will also be presented in a listing.

Descriptive summaries will be provided for ADA by study visit. Number and percentage of participants with positive ADA will also be summarized by study week. Unscheduled assessments will also be presented. Data will also be presented in a listing.

One line plot will be generated, plotting FVIII activity level at Week 52 based on central chromogenic assay against ADA titer at Screening visit and ADA titer at Week 52, respectively.

Number and percentage of participants with FVIII inhibitor by the Bethesda Assay will be summarized by study visit.

6.7. COVID-19 Related Data

In the event that any of the safety and/or efficacy related postinfusion procedures for ECG, liver ultrasound, HJHS, or PROs cannot be performed according to the timepoints specified in the study protocol, due to coronavirus disease 2019 (COVID-19) restrictions or otherwise, it is recommended that they be performed at the next subsequent on-site visit or unplanned visit. Even though the procedures may have been performed at a subsequent visit, any procedures not performed according to the timepoints specified in the study protocol are still considered protocol violations.

The impact of COVID-19 on C3731003 is expected to be minimal. The related data will be provided in the following data listings:

- Protocol deviations related to COVID-19.
- COVID-19 related adverse events will be listed with SOC and PT.
- Any study discontinuation due to COVID-19 related AEs, SAEs or death related to COVID-19.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be performed. 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

Not applicable.

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8. REFERENCES

1. Hendriek C Boshuizen and Edith JM Feskens "Fitting additive Poinsson models" Epidemiologic Perspectives & Innovations 2010, 7:4.

2. Mark W. Donodhoe and Ian C. Marschner "Estimation of adjusted rate differences using additive negative binomial regression" Statistics in Medicine Research Article published online 12 April 2016 (wileyonlinelibrary.com) DOI: 10.1002/sim.6960.

3. Nicolaides NC, Pavlaki AN, Maria Alexandra MA, et al. Glucocorticoid Therapy and Adrenal Suppression. [Updated 2018 Oct 19]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279156/

4. Budesonide product label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021324s009lbl.pdf

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9. APPENDICES

Appendix 1. Statistical Methodology Details

Appendix 1.1. Specification for ABR Analysis Model and Parameters

The specific model parameters are:

- Response variable: observed number of bleeds, Y_i, where Y_i is assumed to follow negative binomial distribution
- Link function: Identity; $E[Y_i] = \mu_i = \eta_i$
- Linear predictor model: the mean number of bleeds is proportional to the observed duration, allowing for a different ABR per treatment;

  $\eta_i = \beta_1 \cdot t_i + \beta_2 \cdot I(\text{Treatment}) \cdot t_i$; t_i = duration of observation in years
- Assumed variance-covariance: The working correlation is assumed as *unstructured*, so that the variance of Y_i is given by:

  $V(Y_i) = \begin{bmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{12} & \sigma_{22} \end{bmatrix}$.

  Since there are only two data points per participant, many assumptions for the working correlation except for independence will result in the same estimate.
- The log link is commonly used in the generalized linear mixed model for the count data with a negative binomial distribution. However, identity link could also be applied to model count data, for Poisson distribution[1] and negative binomial distribution[2] when rate difference is of interest. The identity link was chosen to match the analysis goal, the testing of non-inferiority based on the difference in annualized bleeding rates (ABRs) between the two treatments for the participants that received different treatments before and after rather than the ratio of the two. In the above linear predictor model, β_2 represents the ABR difference.

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Appendix 1.2. Example of SAS Code for Repeated Measure Additive Negative Binomial Regression Model

```
proc genmod data=main;
class trt subjid;
model bleeds = years years*trt/link=identity dist=negbin noint;
repeated subject=subjid;
estimate ‘diff’ years*trt 1 -1/alpha=0.05;
estimate 'Prophy' years 1 years*trt 0 1 / alpha=0.05;
estimate 'GTx' years 1 years*trt 1 0 / alpha=0.05;
Run;
```

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Appendix 1.3. Example of SAS Code for Calculating Percent Reduction in Mean ABR

```
proc genmod data=main;
class trt subjid;
model bleeds = trt /offset=lyears dist=negbin link=log alpha=0.05;
** offset=log of years **;
repeated subject=subjid/ Type=UN;
estimate 'log diff' trt 1 -1 / exp;
ods output estimate=ci_ratio;
run;

data ci_reduction;
set ci_ratio;
where  Label= "Exp(log diff)";
Percent_reduction = (1- LBetaEstimate)*100;
Lower_bound = (1- LBetaUpperCL)*100;
Upper_bound = (1- LBetaLowerCL)*100;
run;
```

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Appendix 1.4. Additional US-specific Analyses

Total ABR:

Supplementary analysis: Repeat the same analysis model and summary for the main analysis as described in Section 6.1.1.1 on the Total ABR from Week 12 through data cutoff using the 'Dosed' population regardless of the length of follow-up preinfusion or postinfusion. In addition, the imputation rule per given event below in Table 10 will be applied.

Table 10. Imputation Rules for US-Specific Analysis of Total ABR

Event	Imputation Rule
Resumption of prophylaxis regimen	The Total ABR post prophylaxis resumption date through data cutoff will be imputed with 35.
Taking FVIII infusions post PF-07055480 infusion for a time period in a manner similar to prophylaxis regimen (Note: these events will be identified based on clinical review.)	The Total ABR during this period will be imputed with 35.

If a participant resumes prophylaxis regimen and then later discontinues from the study prior to data cutoff, his Total ABR post prophylaxis resumption data through data cutoff will be imputed with 35 (i.e., the imputation rule will be applied for the period from study discontinuation to data cutoff).

The corresponding supplementary estimand is the treatment effect of PF-07055480 compared to routine prophylaxis with respect to Total ABR (treated and untreated bleeds) after prior prophylaxis treatment is stopped following infusion, from Week 12 [Day 78] through data cutoff.

Table 11. Supplementary Estimand of Total ABR

Estimand Attribute	Description
Population	Male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII:C ≤1%), who have tested negative for anti-AAV6 nAb and have no medical history of FVIII inhibitor.
Variable	Total ABR (treated and untreated bleedings) from Week 12 [Day 78] through data cutoff post PF-07055480 infusion.
Intercurrent Event	• Data post prophylaxis resumption date through data cutoff will be imputed. • Data during a time period when the participant was taking FVIII infusion in a manner similar to prophylaxis regimen will be imputed. • Data after study discontinuation will not be imputed unless prophylaxis was resumed prior to discontinuation.

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Estimand Attribute	Description
Population-Level Summary	Total ABR post PF-07055480 infusion will be compared to participants' Total ABR on prior FVIII prophylaxis regimen using a repeated measure negative binomial regression model. Model-based estimated difference in mean Total ABR and the 95% CI will be reported. In addition, percent reduction in mean Total ABR and the corresponding 95% CI will be estimated.

A sensitivity analysis to repeat the same analysis model and summary as described in Section 6.1.1.1 on the Total ABR from Week 12 through at least 15 months (up to data cutoff) using the 'Efficacy' population and apply the imputation rules described above.

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Appendix 2. Summary of Efficacy/PRO Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation won't be imputed.	A generalized linear model with repeated measures with negative binomial distribution and identity link function to demonstrate non-inferiority to prior FVIII prophylaxis regimen with a NI margin of 3.0 bleeds/year. If noninferiority is demonstrated, further testing for superiority would be conducted.
Total ABR (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Dosed	Same as for the main analysis.	Same as above but no hypothesis testing.
Total ABR (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Evaluable	Same as for the main analysis.	Same as above but no hypothesis testing.
Total ABR postinfusion (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) compared to separately the first and the latest 6 months preinfusion data	Primary analysis: sensitivity analysis	Efficacy	Same as for the main analysis. To include the bleeding data collected during only the latest 6 months and the first 6 months separately during the lead-in study up to preinfusion of PF-07055480 in the 'Efficacy' population.	Same as above but no hypothesis testing.
Total ABR postinfusion (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Efficacy	Same as for the main analysis. Include only the data collected in the lead-in study (C0371004) and the data postinfusion of PF-07055480 in the 'Efficacy' population.	Same as above but no hypothesis testing.

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
compared to the data collected in the lead-in study.				
Total ABR postinfusion (from Week 12 through data cutoff postinfusion of PF-07055480) with imputation	US-specific analysis	Dosed	Same as for the main analysis and the imputation rules described in Table 10 will be applied.	Same as for the main analysis with hypothesis testing.
Total ABR postinfusion (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) with imputation	US-specific analysis: supplementary	Efficacy	Same as for the main analysis and the imputation rules described in Table 10 will be applied.	Same as for the main analysis with hypothesis testing.
Assessment of treatment failure	Primary analysis: supplementary analysis	Dosed	Details are described in Section 6.1.1.3.	Participant-level data listing.
FVIII activity level > 5% at 15 months postinfusion of PF-07055480	Primary analysis: main analysis	Efficacy	• Any sample taken within 72 hours after administering standard half-life exogenous FVIII replacement therapy, or 120 hours for products with extended half-life, for any purpose (including treatment of bleeding or prevention purposes) will be excluded. • Participants who resume prophylaxis regimen prior to reaching Month 15 visit will be considered as having FVIII activity level ≤5%. • Participants who discontinue from the study prior to reaching Month 15 visit will be considered as having FVIII activity level ≤5%. • Missing FVIII activity level will be imputed with the earliest FVIII level collected post Week 65 (Month 15) visit	Exact test for binomial proportion

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
			window. In case there are no FVIII activity levels collected post Week 65 visit window but the participant has not discontinued from the study, the FVIII activity level will be considered as missing and excluded from the analysis.	
FVIII activity level <1%, 1-5%, >5-<15%, 15-<40%, 40-≤150%, >150% at Week 12, Week 26 (Month 6), Week 52 (Month 12), Month 15, Month 18, Year 2, Year 3 postinfusion	Primary analysis: sensitivity analysis	Dosed	See imputation rules described in Section 3.2.5.	Number (%) of participants
Treated ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation will not be imputed.	Same as above for Total ABR from Week 12 through at least 15 months (up to data cutoff).
Treated ABR (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Dosed	Same as above.	Same as above for Total ABR from Week 12 through at least 15 months except no hypothesis testing.
Treated ABR (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Evaluable	Same as above.	Same as above for Total ABR from Week 12 through at least 15 months except no hypothesis testing.
FVIII activity level from Week 12 through 15 months postinfusion of PF-07055480	Primary analysis: main analysis	Efficacy	See imputation rules described in Section 3.2.4.	FVIII activity from Week 12 through 15 months postinfusion in a participant will be calculated as a geometric mean of evaluable FVIII activity levels collected during the specified

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
				time period. Descriptive statistics, 95% CI of mean.
FVIII activity by visit	Primary analysis: main analysis	Dosed	See imputation rules described in Section 3.2.5.	Descriptive statistics, 95% CI of mean. Number (%) of participants with FVIII activity ≥ 40%.
FVIII activity at Weeks 26, 52 (Month 12), 65 (Month 15), 104 (Year 2), and 156 (Year 3).	Primary analysis: sensitivity analysis	Dosed	Same as above.	Order statistics (consisting of minimum, percentiles at 10%, 25%, 50%, 75%, and 90%, and maximum).
AIR of exogenous FVIII (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	No imputation for missing data.	P-value from the paired t-test. Descriptive statistics and 95% CI of means and mean difference.
AIR of exogenous FVIII (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Dosed	No imputation for missing data.	Same as above.
AIR of exogenous FVIII (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) vs AIR in the lead-in study only	Primary analysis: sensitivity analysis	Efficacy	No imputation for missing data.	Same as above.
Annualized FVIII consumption (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	No imputation for missing data.	P-value from the paired t-test. Descriptive statistics and 95% CI of means and mean difference.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Annualized FVIII consumption (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) vs annualized FVIII consumption in the lead-in study only	Primary analysis: sensitivity analysis	Efficacy	No imputation for missing data.	Same as above.
Annualized FVIII consumption (from Week 12 through data cutoff postinfusion of PF-07055480) vs annualized FVIII consumption in the lead-in study only	Primary analysis: sensitivity analysis	Dosed	No imputation for missing data.	Same as above.
Treated ABR of specific type (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation will not be imputed.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Treated ABR by cause within each location [i.e., (spontaneous, traumatic) x (joint, target joint, soft tissue/muscle/other)] from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480	Primary analysis: supplementary analysis	Efficacy	Same as above and only postinfusion data will be included.	Descriptive statistics.
Total ABR by cause and by location type (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	Same as above for Total ABR from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Total ABR by cause within each location [i.e., (spontaneous, traumatic) x (joint, target joint, soft tissue/muscle/other)] from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480	Primary analysis: supplementary analysis	Efficacy	Same as above and only postinfusion data will be included.	Descriptive statistics.
Percentage of participants without treated bleeds (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Percentage of participants without treated bleeds (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Percentage of participants without treated or untreated bleeds (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480)	Primary analysis: main analysis	Efficacy	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Percentage of participants without treated or untreated bleeds (from Week 12 through data cutoff postinfusion of PF-07055480)	Primary analysis: sensitivity analysis	Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Change from baseline in joint health as measured by the HJHS instrument by visit through data cutoff postinfusion	Primary analysis: main analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Change from baseline in HaemAQoL by visit through data cutoff postinfusion	Primary analysis: main analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.
Change from baseline in HAL by visit through data cutoff postinfusion	Primary analysis: main analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.
Treated ABR by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation won't be imputed. • Participants who have discontinued from the study or resumed prophylaxis regimen prior to the start of a given yearly interval will be excluded.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Treated ABR by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
FVIII activity level <1%, 1-5%, >5-<15%, 15-<40%, 40-≤150%, >150% at Year 4, and Year 5 (using protocol-defined visit windowing)	Final analysis	Dosed	See imputation rules described in Section 3.2.5.	Number (%) of participants
FVIII activity at Year 4 and Year 5	Final analysis	Dosed	Same as above.	Order statistics (consisting of minimum, percentiles at 10%,

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
				25%, 50%, 75%, and 90%, and maximum).
AIR of exogenous FVIII by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Paired t-test.
AIR of exogenous FVIII by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Paired t-test.
Annualized FVIII consumption by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Paired t-test.
Annualized FVIII consumption by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Paired t-test.
Treated ABR of specific type by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	• Any data after the resumption of FVIII prophylaxis regimen (if necessary) will be excluded. • Data after study discontinuation won't be imputed. • Participants who have discontinued from the study or resumed prophylaxis regimen prior to the start of a given yearly interval will be excluded.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Treated ABR of specific type by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Total ABR (treated and untreated bleedings) by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Total ABR (treated and untreated bleedings) by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Total ABR by cause and by location by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Total ABR by location by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	Same as above.	Same as above for Total ABR (from Week 12 through at least 15 months [up to data cutoff] postinfusion of PF-07055480) but no hypothesis testing.
Percentage of participants without treated bleeds by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Percentage of participants without treated bleeds by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.

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Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
Percentage of participants without treated or untreated bleeds by yearly interval (Month 15, Years 2-5)	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Percentage of participants without treated or untreated bleeds by cumulative follow-up interval	• Primary analysis: supplementary analysis • Final analysis	Efficacy / Dosed	No imputation for missing data.	Number (%) of participants and 95% CI of the observed percentage.
Change from baseline in joint health as measured by the HJHS instrument by visit	Final analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.
Change from baseline in Haem-A-QoL by visit	Final analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.
Change from baseline in HAL by visit	Final analysis	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.
Target joints, baseline target joints resolved, new target joints during the follow-up period through data cutoff post postinfusion and by cumulative follow-up interval	Primary analysis and Final analysis: Tertiary/Exploratory	Dosed	No imputation for missing data.	Number (%) of participants with 0, 1, 2, or ≥3 specified target joints.
Joint status as assessed by X-ray in Pettersson scale: change from baseline in total score, scores at specific joints, and scores at	Final analysis: Tertiary/Exploratory	Joint x-ray substudy	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis
target joints at Week 156 (Year 3) and Week 260 (Year 5 or Early Discontinuation Visit)				change from baseline, and p-value from the paired t-test.
Joint status as assessed by ultrasound based on HEAD-US scoring at Week 24, Week 52 or Early Discontinuation Visit	Primary analysis: Tertiary/Exploratory	Evaluable population in the ultrasound substudy	No imputation for missing data.	Counts and percent for individual items. Total score for each joint will be summarized by visit with descriptive statistics and 95% CI of mean for the observed value and change from baseline.
PGIS and PGIC by visit	Primary analysis and Final analysis: Tertiary/Exploratory	Dosed	No imputation for missing data.	Counts and percent.
HLIQ by visit	Primary analysis and Final analysis: Tertiary/Exploratory	Dosed	No imputation for missing data.	Counts and percent by response to individual items.
Change from baseline in EQ-5D-5L Index score and VAS score by visit	Primary analysis and Final analysis: Tertiary/Exploratory	Dosed	No imputation for missing data.	Descriptive summary, 95% CI of mean for the observed value and change from baseline, and p-value from the paired t-test.

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Appendix 3. List of Abbreviations

Abbreviation	Term
AAV	adeno-associated virus
AAV6	adeno-associated viral vector, serotype 6
ABR	annualized bleeding rate
ADA	anti-drug antibody
AE	adverse event
AFP	α-Fetoprotein
AIR	annualized infusion rate
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BDD	B-domain deleted
BLoQ	Below limit of quantification
CDF	cumulative distribution function
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CS	corticosteroid
DNase	deoxyribonuclease
DOAC	direct oral anticoagulant
ECG	electrocardiogram
eDMC	External Data Monitoring Committee
ELISPOT	Enzyme-Linked Immune-Spot
EOS	end of study
EQ-5D-5L	EuroQol, 5 dimensions, 5 levels
FVIII	coagulation factor VIII
FVIII:C	factor VIII: circulating
Gal3BP	galectin-3-binding protein
GEE	generalized estimating equation
GGT	gamma-glutamyl transferase
Grp78	78-kDa glucose-regulated protein; glucose regulatory protein 78
H	Hemophilia
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HCC	hepatocellular carcinoma
HEAD-US	Haemophilia Early Arthropathy Detection with Ultrasound
hFVIII	human factor VIII
HJHS	Hemophilia Joint Health Score
HLIQ	Hemophilia Life Impacts Questionnaire
HRQoL	health-related quality of life
ICF	informed consent form

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Abbreviation	Term
IFNγ	Interferon gamma
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalized ratio
IU	International unit
LA	left ankle
LDH	lactic acid dehydrogenase
LE	left elbow
LFT	liver function tests
LK	left knee
LLoQ	Lower limit of quantification
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
nAb	neutralizing antibodies
NI	non inferiority
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PF	physical functioning
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PH	physical health
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
qPCR	quantitative real-time polymerase chain reaction
RA	right ankle
RE	right elbow
RK	right knee
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
SOC	standard of care; system organ class for adverse events
SUSAR	Serious Unexpected Suspected Adverse Reaction
TAT	thrombin antithrombin level
TEAE	treatment emergent adverse event
TGA	thrombin generation assay
ULN	upper limit of normal
ULoQ	upper limit of quantification
VAS	visual analogue scale
vg/kg	vector genome per kilogram
WBC	white blood cell

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