TITLE PAGE

Protocol Title: 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%)

Protocol Number: C3731003

Amendment Number: 10

Compound Number: PF-07055480 (formerly SB-525)

Study Phase: Phase 3

Short Title: Not applicable

Acronym: Not applicable

Sponsor Name: Pfizer, Inc.

Legal Registered Address: 66 Hudson Boulevard East, New York, NY 10001

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Will be provided separately.

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Amendment 10	28 September 2023
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Amendment 3	12 Mar 2021
Amendment 2	09 December 2020
Amendment 1	13 May 2020
Original protocol	10 December 2019

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 10 (28 September 2023)

Overall Rationale for the Amendment: Changes in the Primary analysis to allow the inclusion of additional data to at least Month 15, according to feedback from regulatory agency:

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Modification of the main analysis for Total ABR to include all available data from Week 12 through at least Month 15 up to the primary analysis data cutoff. For consistency, the same change has been applied to the key secondary endpoint of ABR and the secondary endpoints of AIR, Annualized FVIII	To support a comprehensive assessment of total ABR and other related endpoints, by increasing the time frame of included data, in line with regulatory feedback. There is no change to the timepoint for the primary analysis for the study.	1.1 Synopsis 2.1 Study rationale 3. Objectives, Estimands, and Endpoints 4.1 Overall design 9.1.1. Estimands 9.4.1. Efficacy analysis

Description of Change	Brief Rationale	Section # and Name
consumption, ABR of specific type, Total ABR by cause and by location and Percentage of participants without bleeds.		
Updated required wash-out period for extended half-life FVIII product from 96h to 120h before testing of FVIII activity, FVIII inhibitors and hemostasis and thrombophilia-related factors. Similar rules have been applied for the statistical analysis of FVIII activity-related endpoints to exclude from the assessments any samples taken within 72 hours for standard half-life products and 120 hours for extended half-life products (currently 96 hours regardless of half-life) after administration of exogenous FVIII replacement therapy for any purpose.	Take into account the difference in half-lives between FVIII products.	1.3. Scope of Activities 3. Objectives, Estimands, and Endpoints 9.1.1. Estimands
Non-substantial Modification(s)		
Updated the domain names in Haem-A-QoL.	Changes made to reflect the latest information on this PRO	8.1.4.1 Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)
Clarification that any tissue collected in the context of a safety investigation as further described in this section might be assessed for integration, as already indicated in the ICF.	Text initially erroneously described in Section 8.2.4. moved to a new section 8.2.5. Samples for Other Vector Integration Related Testing (if applicable). Minor clarification added.	8.2.5. Samples for Other Vector Integration Related Testing (if applicable).

Description of Change	Brief Rationale	Section # and Name
Added antifibrinolytics (aminocaproic acid and tranexamic acid) to the list of disallowed therapies for this study.	For clarity and consistency with the design/purpose of the study (there is no change to the study eligibility /conduct).	6.5.2. Disallowed therapy.
Added to the synopsis sections regarding study population, statistical methods and ethical considerations	To ensure consistency/compliance with Pfizer's protocol template	1.1.Synopsis 10.10. Appendix 10. Protocol amendment history
Minor changes to the statistical wording	For consistency with SAP	3. Objectives, Estimands, and Endpoints 9.1.1. Estimands 9.4. Statistical analysis
Editorial changes, deletion of redundant text	For consistency, clarity and to ensure compliance with Pfizer's protocol template	3. Objectives, Estimands, and Endpoints 9.1.1. Estimands 10.1 Regulatory, Ethical, and Study oversight consideration

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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%)
Short Title: Not applicable

Rationale:
Sangamo Therapeutics has developed SB-525 (hereafter PF-07055480), a recombinant adeno-associated virus 6 (rAAV6) capsid and cDNA encoding for the BDD hFVIII. It encodes a liver-specific promoter module and rAAV6 exhibits liver tropism, thus providing the potential for sustained hepatic production of FVIII in hemophilia A participants to reduce or eliminate the need for FVIII replacement therapy.

PF-07055480 is being evaluated in an open-label, adaptive, dose-ranging Phase 1/2 study (SB-525-1603 [hereafter C3731001]) to assess the safety and tolerability in male participants ≥18 years of age with severe hemophilia A. The preliminary data from the Phase 1/2 study indicate that treatment of hemophilia A with PF-07055480 offers clinical advantage over routine prophylactic treatment with FVIII. Specifically, these data indicate that treatment of hemophilia A with PF-07055480 is well tolerated and demonstrated a dose-dependent increase in FVIII levels, achieving clinically relevant increases in FVIII activity in the higher dose cohorts and at or near normal FVIII levels in the 3×10^{13} vg/kg highest dose cohort (normal range: 50-150%). In the highest dose cohort, participants did not require factor replacement therapy (after initial use of prophylactic factor) and experienced no bleeding events in the first year post dosing.

The Phase 3 program includes 2 separate studies: a non-IMP lead-in study (C0371004), where data will be prospectively collected in the context of routine prophylaxis with FVIII products, and this C3731003 pivotal Phase 3 dosing study.

C3731003 pivotal Phase 3 study will further evaluate the clinical efficacy and safety of PF-07055480 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). 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 primary analysis will be conducted when at least 50 dosed participants have reached at least 15 months of follow-up postinfusion (ie, the data cutoff for the primary analysis), 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 (ie, approximately 3 months) for the primary analysis.

The primary endpoint in this study (C3731003) will be the Total ABR, including both treated and untreated bleeding events, through at least 15 months postinfusion, and it will be compared with prior routine prophylaxis. The Total ABR will be assessed from Week 12 through at least 15 months postinfusion in at least 50 dosed participants.

FVIII activity level >5% at 15 months postinfusion will be a key secondary endpoint. The other key secondary endpoint is the ABR (treated bleeding events) from Week 12 through at least 15 months postinfusion in at least 50 dosed participants, compared to preinfusion prophylaxis.

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

Objectives, Estimands, and Endpoints:

Primary Efficacy Objective	**Primary Endpoint and Key Secondary Endpoints**
• 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 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.	• 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 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 compared with prior FVIII prophylaxis replacement regimen: • Annualized FVIII consumption • 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 HJHS instrument. • Change from baseline in the following PRO endpoints: o Haem-A-QoL. o 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: • ABR. • FVIII activity level. • AIR of exogenous FVIII. • Annualized FVIII consumption. • ABR of specific type: o by cause (spontaneous or traumatic). o 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, ABR, Total ABR, and AIR will be analyzed throughout the 5-year study period.
Secondary Safety Objectives	**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 AEs. • Events of special interest (such as hypersensitivity reactions, clinically reported thrombotic events, and malignancy). • Immunogenicity: o Antibodies against AAV6 capsid protein (nAbs and ADAs).

	○ T-cell responses against AAV6 capsid and against the transgene. ○ FVIII inhibitors.

Overall Design

C3731003 is a pivotal Phase 3 study to evaluate the clinical efficacy and safety of a single IV infusion of PF-07055480 in adult male participants with moderately severe or severe hemophilia A (FVIII:C≤1%) for the study duration of 5 years. The study will enroll eligible participants who were followed on routine prophylaxis with FVIII products in the non-IMP lead-in Study C0371004. After this 5-year follow-up period in Study C3731003, participants will be invited to enter a separate study to assess the long-term safety and effectiveness of PF-07055480 for the treatment of hemophilia A for a total of up to 10 additional years, corresponding to up to 15 years post-PF-07055480 infusion.

Disclosure Statement

This is a Single Group Treatment study with 1 Arm that has No masking.

Number of Participants

Approximately 70 participants from the lead-in Study C0371004 will be enrolled to achieve at least 50 dosed participants completing at least 15 months of follow-up postinfusion.

Study population

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Participant must be ≥18 and <65 years of age at the time of signing the informed consent.

2. Participants must have been followed on routine FVIII prophylaxis therapy in the lead-in study (C0371004) and have ≥150 documented exposure days to a FVIII protein product (standard half-life or extended half-life recombinant, plasma derived).
3. Participants who have documented moderately severe to severe hemophilia A defined as circulating FVIII activity levels ≤1%.
4. Participants must agree to suspend prophylaxis therapy for hemophilia A after administration of the study intervention (see guidance in general notes of SoA). FVIII replacement therapy is allowed as needed (see Section 6.5.1).

5. Acceptable screening central laboratory values as follows:
    - Hemoglobin ≥11 g/dL
    - Platelets ≥100,000 cells/µL;
    - Creatinine ≤2.0 mg/dL.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Anti-AAV6 nAb titers, above or equal to the established threshold of 1:4, performed by a central laboratory during screening**.**
2. Prior history of FVIII inhibitor (clinical or laboratory-based assessment) defined as a titer ≥0.6 BU/mL
3. Known hypersensitivity to FVIII replacement product or intravenous immunoglobulin administration.
4. History of chronic infection or other chronic disease that investigator deems an unacceptable risk. In addition, any participant with conditions associated with increased thromboembolic risk such as inherited or acquired thrombophilia, or a history of thrombotic events, including but not limited to stroke, myocardial infarction, or venous thromboembolism, is excluded.
5. ALT, AST, ALP >2x ULN, based on central laboratory results.
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%), based on central laboratory results.
7. Active hepatitis B or C:
    - HBcAb, HBsAg, and HBV DNA positivity. Exception: if a participant is positive for HBcAb, then HBsAg and HBV DNA must be negative for inclusion.
    - HCV-RNA positivity.
8. Significant liver disease, defined by pre-existing diagnosis of portal hypertension, splenomegaly or hepatic encephalopathy.
9. Serological evidence of HIV-1 or HIV-2 with either CD4+ cell count ≤200 mm^3 or viral load >20 copies/mL.

Intervention Groups and Duration

The study treatment, a single infusion of PF-07055480, a gene transfer agent, will be administered on Day 1 at a dose of 3 x 10^{13} vg/kg of body weight.

The safety and efficacy data will be collected over 5 years as described in the SoA included in Section 1.3.

Data Monitoring Committee: Yes

Statistical Methods:
The primary endpoint and the associated hypothesis testing is to demonstrate NI of PF-07055480 to routine prophylaxis on the difference in Total ABR (NI margin of 3 bleeds/year) by comparison of postinfusion of PF-07055480 Total ABR (through at least 15 months up to data cutoff) versus prestudy intervention infusion Total ABR collected during the lead-in study (C0371004) and preinfusion of PF-07055480 in this study (C3731003), in male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII activity ≤1%), who have tested negative for nAb, to AAV6 and have no medical history of FVIII inhibitor.

A gatekeeping process will be applied to control for multiple endpoint comparisons at the primary analysis which is planned after at least 15 months of follow-up postinfusion in at least 50 dosed participants who have completed at least 6 months in the lead-in study (C0371004). The subsequent hypothesis testing will only be performed after success on the previous hypothesis test. The sequence of gatekeeping process and details of statistical methodology will be specified in the SAP.

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

Ethical Considerations:
The major benefit of gene therapy is that it may provide persistent treatment of hemophilia by continuous endogenous production of functional FVIII, providing therapeutic effect and a relief from the medical and lifestyle burden of recurrent on demand or routine prophylactic protein replacement therapy. By providing a stable production of serum FVIII levels, protection for bleeding episodes may be provided. Although replacement therapy increases FVIII levels in the bloodstream, these levels include peaks and troughs that are non physiological and lead to less protection before the next infusion. Gene therapy may also favourably impact the recognised complications of hemophilia: recurrent hemarthroses and the subsequent arthropathy. It is feasible that gene therapy treatment may result in expression of FVIII consistent with conversion from a moderate or severe to a mild hemophilia or better, persisting for at least a decade.

Identified and main potential risks associated with PF-07055480 include: **Identified risks:**

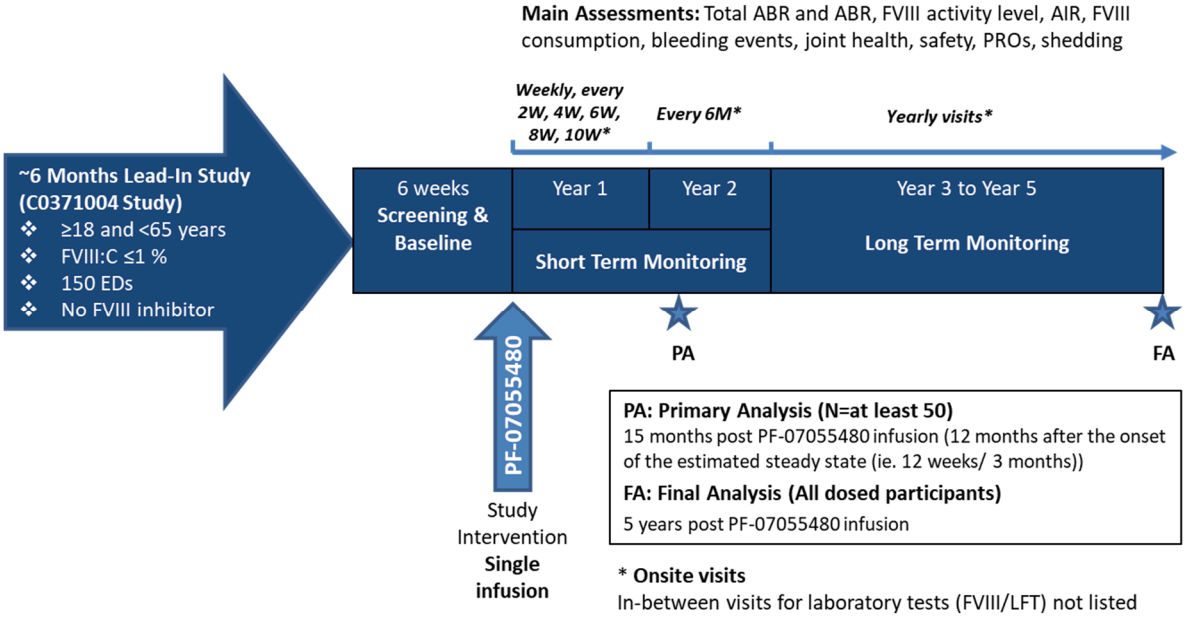
- Infusion reactions (including hypersensitivity): PF-07055480 may include infusion-related reactions (IRRs) which may be due to immune reactions and/or allergic reactions/ hypersensitivity and lead to fever, chills, tachycardia, headache, nausea, vomiting or hypotension.

Main Potential risks:

- Hepatotoxicity: there is a potential risk of liver inflammation for this liver-tropic viral vector due to activation of the immune system in the liver. Liver inflammation can be detected by elevated blood liver enzymes (transaminases; ALT and/or AST).
- Neutralizing antibodies to AAV6 since administration of AAV vectors leads to humoral immune response to AAV.
- FVIII Inhibitors: antibodies to FVIII that neutralize the clotting activity of FVIII after administration of FVIII are a known complication in 25-30% of severe hemophilia A patients.
- Thromboembolic events: This is related to potential FVIII activity levels >ULN post IP infusion.
- Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07055480 are justified by the anticipated benefits that may be afforded to participants with hemophilia A.

1.2. Schema

Figure 1 C3731003: Study Design



1.3. Schedule of Activities (SoA)

General Notes:

The screening and baseline period may be extended after consulting with the sponsor's medical monitor. The reason must be recorded in the source documents. Depending on the length of extension (of either period), the medical monitor may request to have visit procedures repeated.

- **FVIII prophylaxis recommendations**:
  - FVIII prophylaxis is authorized during screening and baseline period, but perform FVIII activity, inhibitor and hemostasis assays in the absence of residual infused FVIII (recommended washout is 72 h for standard half-life FVIII products and 120 h for extended half-life FVIII products).
  - Schedule the FVIII infusions so that a FVIII infusion is performed on Day 1 (before study intervention).
  - After study intervention is administered, prophylaxis is recommended for 2 weeks.

Study sites without necessary infusion facilities will complete Visits 1-2 at the study site and Visit 3 (Day 1) will be completed at the designated **infusion center**.

Unscheduled visits may be necessary for safety monitoring or to repeat any blood sampling if required.

Early discontinuation visit should follow the procedures for Week 260 visit. Discuss participant management and risks inherent with discontinuation with the sponsor's medical monitor.

Alternative study measures during the COVID-19 Pandemic are described in Appendix 9.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after study intervention[#]	Week -6 to Week -3	Week -3 to Day 1	Day 1**	1	2	4	8	12	18	24	32	42	52	
Informed consent	X													Must be obtained before any study-related procedures. Two ICFs may be required, one from the study site and the other from the infusion center (if applicable).
Assess/confirm eligibility (inclusion and exclusion criteria)	X*	X*	X[#]											*Review and confirm eligibility criteria (see Section 5.1 and Section 5.2) before ordering the study intervention at the beginning of the baseline period. [#]Review and confirm eligibility (see Section 5.1 and Section 5.2) before infusion. The infusion center should confirm eligibility with study site.
Demographics, medical, surgical, and hemophilia history	X													All ongoing AEs and SAEs, including AEs of special interest, in the lead-in study (C0371004) will be collected as medical history for this study. Only changes to historical data on medical, surgical and hemophilia history will be captured. Any new AEs/SAEs after completion of the lead-in study will follow the AE reporting process (Section 8.3.1, Appendix 3).

Procedures Year 1	Screening Period	Baseline Period	Study Intervention	Week 1-12 (±2 days)					Weeks 13-52 (±1 week)					
Physical exam, height*, weight, and vital signs	X*	X	X[#]	X	X	X	X	X	X	X	X	X	X	Complete a physical exam at all clinic visits. *Height is required to be collected at the screening visit only. Weight must be obtained at the screening visit to order the correct quantity of study intervention and to calculate the dose (Section 8.2.1). Vital signs include body temperature (°C), pulse rate, respiratory rate, and blood pressure (systolic and diastolic), after at least 5 mins rest in supine or upright/sitting position. [#]On Day 1, vital signs will be obtained: • before study intervention infusion; • within 5 min of start of study intervention infusion; • every 15 [±5] minutes for the length of the study intervention infusion, every 15 [±5] minutes until stable (±10 mmHg), then every 30 [±5] minutes until 2 hours after infusion completion, then every 4 hours [±10 min] until discharge. Please note: Study intervention infusion may take several hours. Completion of study intervention infusion is defined as study intervention infusion and IV line flush. Vital signs will also be performed 24 h [±3] h after completion of infusion and before hospital discharge.

- [#] The schedule of assessments should be based on Day 1.
- ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA.
- ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned.
- **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection).
- **Clinical decisions** may be based on **local or central laboratory assessments**.
- Refer also to the General Notes at the beginning of the SoA.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Cardiac monitoring: Local ECG* Troponin I (CL)[#]	X*	X[#]					X[#] (Wk 6 and 12 only)		X[#]				X *	*ECG: • Local single 12-lead ECG. Additional single ECGs may be obtained as clinically indicated. If an ECG cannot be performed at Visit 13, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit. [#]Troponin I: • Troponin I (high sensitivity Troponin I assay) to be assessed at baseline and Weeks 6, 12, and 18. During study: troponin I to be performed whenever an LFT increase occurs and is associated with a suspected T-Cell response. ○ If troponin is elevated (ie, >99th percentile), repeat the assay for confirmation. ○ If troponin I elevation is confirmed, then arrange an ECG and cardiology consultation.
Target joint assessment	X													See for definition of a target joint. Done as part of hemophilia history.
Joint X-ray*	X#													*Some participants (except in Germany) who consent to participate in an optional substudy will undergo X-ray for assessment of joints (Section 8.1.3.3). Central reading will be performed (Pettersson score). # If this X-ray cannot be performed during the screening period, it is acceptable to postpone this testing no later than Week 4 / Visit 6.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ # The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Joint ultrasound*		X#								X			X	*Some participants (n~20) who consent to participate in an optional substudy will undergo joint ultrasound (Section 8.1.3.2). # If this ultrasound cannot be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4 / Visit 6.
Hepatitis/HIV screening (CL) and liver fibrosis testing (CL)	X													Hepatitis B and C: HBsAg, HBcAb, HBV-DNA; HCV-RNA Quantitative HIV: Antibody testing. If positive antibodies, CD4+ count and HIV viral load. Liver fibrosis: FibroScan, or FibroTest/FibroSURE. FibroScan, if performed, would be performed locally (fasting recommended).
α-fetoprotein (CL)	X												X	To be tested as biomarker for hepatic carcinoma.
FVIII genetic testing (CL)	X*													*To be performed if not performed before and/or result not available in medical file.
FVIII inhibitor testing (CL, test in LL if clinically necessary)	X*				X	X	X	X	X	X	X	X	X	**Samples should be collected in the absence of residual infused FVIII product** (recommended washout is 72 h for standard half-life FVIII products and120 h for extended half-life FVIII products). *Positive inhibitor testing as measured by the central laboratory ≥0.6 BU at Visit 1 would be exclusionary. Nijmegen Bethesda Inhibitor assay to be done at the central laboratory unless testing at a local laboratory is necessary due to a clinical concern.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ # The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Neutralizing antibodies to AAV6 and other AAVs (CL)	X*												X	Collect blood for serum samples preparation. *Participants with anti-AAV6 nAb titer ≥1:4 are to be excluded from the study. nAb against other AAVs serotypes may be tested on same sample to assess cross reactivity.
Anti-drug antibody (CL)	X												X	Anti-PF-07055480 antibodies. • Collect blood for serum samples preparation.
Laboratory safety panels: hematology and clinical chemistry (CL)	X*				X	X	X	X	X	X	X	X	X	• See Appendix 2 for a full list. • *ABO blood group planned at screening only if unknown.
Laboratory safety panels: lipid panel and urinalysis (CL)	X												X	See Appendix 2 for a full list. At least 8 hours of fasting is required for lipid panel blood collection.
FVIII activity (CL, LL), LFT (CL, LL) and FVIII antigen (CL)	X		X*	Day 1 to Week 12: FVIII activity and LFT: at least 2 times every week starting from Day 1 FVIII antigen: weekly testing starting from Day 1					Week 13 to 20: **FVIII activity: weekly and LFT:** 2 times weekly **FVIII antigen:** weekly Week 22 to 34: **FVIII activity and LFT: every 2 weeks** (Weeks					•**LFT**: See Appendix 2 for a full list. •*** Collect blood for local and central LFTs prior to dosing (up to 3 days prior to Day 1/Visit 3 is acceptable).** Utilize mobile phlebotomy as needed. Local LFTs have to be reviewed before dosing and prior to thawing drug. If the investigator has any clinical concerns regarding the local LFT results, drug should not be thawed. These LFT results may help in the assessment of future LFTs and decisions on when to begin corticosteroid treatment, if necessary. FVIII activity testing on Day 1 is optional.

Procedures Year 1	Screening Period	Baseline Period	Study Intervention	Week 1-12 (±2 days)	Weeks 13-52 (±1 week)	
						○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
				Home health/mobile phlebotomy services allowed.	22, 24 (onsite), 26, 28, 30, 32 (onsite), 34) **FVIII antigen:** approximately monthly (Weeks 24 (onsite), 28, 32 (onsite), and 34) Week 38 to 52: **FVIII activity, FVIII antigen and LFT:** approximately monthly Weeks 38, 42 (onsite), 48, 52 (onsite) Home health/mobile phlebotomy services are allowed.	• **Any FVIII activity and LFT testing will be conducted at local and central lab for all time points and as clinically necessary (also applicable to unscheduled or repeated tests)**. • LFT and FVIII activity obtained at local labs may be used for clinical decisions (as identification of changes suggestive of T-cell reactions and initiation of corticosteroids – see also Section 8.3.10). • FVIII antigen testing will be conducted ONLY at central lab for all time points and as clinically necessary. • FVIII activity should be collected in the **absence of residual infused FVIII** (recommended washout is 72 h for standard half-life FVIII products and 120 h for extended half-life FVIII products)**.** • FVIII activity should be measured in the event of an untreated bleed, as close to the bleeding event as possible. If the bleed necessitates exogenous FVIII, FVIII activity should be assessed post clearance of FVIII product. See also Section 8.1.2. • It is recommended to repeat FVIII activity assessment anytime if there is a significant decrease (not attributed to standard fluctuation or to variability of assays) as assessed by the investigator. The medical monitor may be consulted as needed. See also Section 8.1.2. • **Frequency of FVIII activity and LFT monitoring:** • First 12 weeks: at least 2 times every week due to potential rise in hepatic transaminases and/or loss of FVIII transgene expression. • Week 13 to Week 20: FVIII activity weekly and LFTs 2 times per week. • Week 22 to Week 34: every 2 weeks. • Week 38 to Week 52: approximately monthly. • **Frequency of FVIII antigen:** weekly until Week 20, and then monthly.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ # The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
														• Sponsor recommends collecting specimens Monday through Thursday so results are available before the weekend. • It is highly recommended that participants be provided with a **prednisone prescription** before dosing so that it can be filled and ready should treatment be needed. • It is highly recommended that participants who are initiated on corticosteroid treatment be treated with a **gastric acid reducer**, preferably a proton pump inhibitor (PPI) (eg, omeprazole), or alternatively a histamine type 2 (H2) antagonist (eg, famotidine) for the duration of the corticosteroid course. • FVIII recovery may be tested if prophylaxis is resumed and/or if prophylaxis is administered prior to a surgical procedure. Refer to Section 8.1.2 for more guidance. • Refer to Section 8.3.10 for more guidance about elevated liver enzymes and/or optimization of immunomodulation. Note: if corticosteroid therapy is started, measurement of LFT and of FVIII activity is recommended at least 2 times per week until the end of this therapy. • Refer to Sections 8.1.2 and 8.2.7 for more guidance on how to manage participants with FVIII activity levels >ULN. See also the separate "Management Guide for Elevated Factor VIII Activity Levels".
Request delivery of study intervention from sponsor		X												Order the study intervention at the beginning of the baseline period after confirming eligibility criteria. The study intervention will take approximately 3 weeks for delivery. Prior to IP ordering, consider Sections 10.9.1 and 10.9.6.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Immunology – ELISPOT (PBMC) (CL)		X		Only if corticosteroid treatment is needed for a suspected T-cell response.										• Collect blood for PBMC preparation and ELISPOT assay at baseline and if the corticosteroid treatment is needed for a suspected T-cell response. • Collect specimens before initiating the corticosteroid treatment. If specimens are not collected before initiation, then collect the specimens within 24 hours of administering corticosteroids. • Collect specimens approximately 3 weeks after steroid administration and at the end of the weaning time. Additional specimens may be recommended by the sponsor, in consultation with the investigator, depending on the participant's response to corticosteroid therapy.
Exploratory immunology – other cell mediated assays (PBMC) (CL)	X				X	X	X	X					X	Collect blood for PBMC preparation for cell-mediated exploratory immunology assays.
Exploratory immunology: binding IgG vs IgM antibody response (CL)		X		X	X									Collect blood for serum samples preparation.
Von Willebrand factor (CL)		X		X		X		X	X	X	X	X	X	Collect blood for plasma sample preparation.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					
														○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Spare plasma	X	X	X	X	X	X	X	X	X	X	X	X	X	Draw approximately 5 mL of blood to prepare approximately 2 mL of plasma at each timepoint (when central analyses are done and at least, at each mandatory onsite visit and at each laboratory visit for ALT / FVIII assessment from Week 32 and until the End of Study Visit). The pre-dose 5 mL blood sample to be collected on Day 1* (or -3 Days before Day 1) will be used to prepare approximately 2 mL of serum. Plasma/serum will be stored for repeat or additional testing (including exploratory biomarkers to assess immune response and study intervention mechanism of action) (Section 8.10.3 and Section 8.10.4).
Liver ultrasound	X												X *	Refer to Section 8.2.4 and to the liver ultrasound scanning guidance. *If an ultrasound cannot be performed at Visit 13, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Global hemostasis and thrombophilia-related markers (CL)	X*		X										X	•See Appendix 2 for a full list of possible markers and Section 8.2.8 for more information. •These samples should be collected in the absence of residual infused FVIII product (recommended washout is 72 h for standard half-life FVIII products and 120 h for extended half-life FVIII products). •On Day 1, blood samples for TAT will be used to establish baseline value (before FVIII product infusion). •Hemostasis markers should be assessed as clinically indicated throughout the study and are recommended if vector-derived FVIII:C >150% of normal are achieved (Section 8.2.8). •*Defined thrombophilia-related markers are assessed during screening as part of eligibility confirmation and some parameters can be repeated as clinically indicated (not repeated on Day 1 and Week 52). These markers should be assessed at least once in each participant.
Issue the eDiary	X													Provide eDiary and training to operate it, including timing and information to be entered (Section 8.1.1) starting at Visit 1. Participants will enter information as soon as eDiary has been issued.
Review the eDiary		Ongoing (including unscheduled visits)[#]												Review the eDiary at each onsite visit and ensure appropriate entries during unscheduled and scheduled visits. See definitions of Bleeds and Replacement Factor Regimens in Appendix 7. [#]Not applicable for Visit 3 if done at infusion center.

Procedures **Year 1**	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					
FVIII infusion, accountability			X											Prior to dosing, consider Sections 10.9.1 and 10.9.6. On Day 1 a single prophylactic IV infusion of a FVIII product will be administered under medical supervision over a period of approximately 10 minutes at the standard prophylaxis dose for standard half-life products and for extended half-life products (within reasonable margin of error of approximately ±20%). If there is evidence that this dose may place the participant at supratherapeutic FVIII levels, the dose can be adjusted. Participants are expected to bring their current FVIII replacement therapy with them.
Study intervention infusion, accountability			X											After completing the prophylactic FVIII product infusion, participants will receive a single IV infusion of the study intervention by means of an infusion pump. The length of the infusion will depend on the volume received and may last several hours. Please also refer to the IP manual. Refer to the Infusion Reaction Management Guide for recommendations about clinical management before, during, and after infusion. Do not thaw the study intervention before confirming participant eligibility and that the participant is physically present at the site or infusion center. Flush the IV line at the conclusion of the study intervention infusion.
HJHS		X								X *			X *	To be completed by investigator or the designee (Section 8.1.3.1). *If the HJHS cannot be performed at Visit 10 and/or 13, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.

- [#] The schedule of assessments should be based on Day 1.
- ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA.
- ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned.
- **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection).
- **Clinical decisions** may be based on **local or central laboratory assessments**.
- Refer also to the General Notes at the beginning of the SoA.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**					**Weeks 13-52 (±1 week)**					
														○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
PROs		X*						X		X			X	Participants will complete 6 instruments at the site using an electronic tablet: Haem-A-QoL, HAL (v2), HLIQ, EQ-5D-5L, PGIS (n=3), PGIC (n=3). Administer the questionnaires before dosing, treatment, or conversation between the healthcare team and participants about their health condition. See Section 8.1.4 for additional considerations. *PGIC items are not completed at baseline visit 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.
Vector shedding analysis by PCR and infectivity (CL)		X	X*	Weekly, as needed # Or every 2 weeks past Week 20 Home health/mobile phlebotomy services allowed From Week 34, monthly collection is allowed in the absence of home health/mobile phlebotomy services at a site or country										• [#]Collect plasma, PBMC, saliva, semen, and urine specimens at baseline and every week after study intervention until 3 consecutive specimens test negative for the given specimen type. • [#]Collection of blood to prepare PBMCs and assess shedding postinfusion will start from Week 20. • Semen samples may be collected at home the night before a clinic or home health/mobile phlebotomy services visit and stored in the participant's freezer until the clinic or home health/mobile phlebotomy services visit. • *Optional vector shedding sub-study (12 participants): additional samples (plasma, PBMC, saliva, semen and urine) will be collected, onsite only, 2 h [±30 min], 24 h [±3 h], and 72 h [±4 h] after completion of the study intervention infusion/IV line flush. • Infectivity will be performed as applicable. Refer to Section 8.5.1 for additional details.

Procedures Year 1	**Screening Period**	**Baseline Period**	**Study Intervention**	**Week 1-12 (±2 days)**	**Weeks 13-52 (±1 week)**	○ [#] The schedule of assessments should be based on Day 1. ○ ***Visit 4/Week 1**: The participant is not required to appear onsite. If onsite visit: perform all procedures as specified in the SoA. If not onsite visit: collect only all required laboratory specimens as specified in the SoA. ○ ****Day 1:** after end of study intervention infusion, 24 h hospitalization is planned. ○ **Home health/mobile phlebotomy** services may be used for pre-dose LFT blood draw and any time after Study Day 1/Visit 3, as needed (for most biological samples collection). ○ **Clinical decisions** may be based on **local or central laboratory assessments**. ○ Refer also to the General Notes at the beginning of the SoA.
Any additional safety tests	Ongoing (as needed)					Additional laboratory testing or procedures may be conducted as deemed clinically necessary by the investigator to ensure the safety of participants.
Adverse events	Ongoing (including unscheduled visits)					During the short-term monitoring period (up to and including 104 weeks postinfusion) all SAEs and AEs will be collected (Section 8.3.1 and Appendix 3).
Concomitant medications, surgeries, and procedures	Ongoing (including unscheduled visits)					All concomitant therapy will be collected from up to 30 days before screening until the end of the short-term safety monitoring period (104 weeks) (from the lead-in study, when applicable) (see Section 6.5). All procedures and surgeries (including elective surgeries) are to be recorded (see Section 6.5). Note: FVIII product infusions will be recorded in the eDiary.
Optional Liver Biopsy	X (postinfusion)					Participants who consent to participate in this optional substudy will undergo liver biopsy. The biopsy may be performed at any time postinfusion when deemed appropriate by the investigator, and according to Section 8.2.8.

Procedures **Year 2 to Year 5**	**Week 53-104 (± 2 weeks)**		**Week 105-208- (± 3 weeks)**		**EOS or Early Discontinuation Week 260 (± 3 weeks)**	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Study Visit	14	15	16	17	18	
Weeks after study intervention	78	104	156	208	260	
Physical exam, weight, and vital signs	X	X	X	X	X	Complete the physical exam at all visits. Vital signs include blood pressure, pulse rate, respiratory rate, body temperature (°C) after at least 5 mins rest in supine or upright/sitting position.
Cardiac monitoring: Local ECG* Troponin I (CL)[#]		X	X	X	X	*ECG: • Local single 12-lead ECG. • Additional single ECGs as clinically indicated. • Authorized time window for ECG assessment during the long term follow-up period: ±1 month at W104 and ±2 months at W156 and W208. • If the ECG cannot be performed at a visit, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit. #Troponin I: • Troponin I to be performed whenever an LFT increase occurs and is associated with a suspected T-Cell response. ○ If troponin elevated (ie, >99th percentile), repeat the assay for confirmation. ○ If troponin I elevation confirmed, then arrange an ECG and cardiology consultation.
Joint X-ray*			X#		X	*Some participants (except in Germany) who consent to participate in an optional substudy will undergo X-ray for assessment of joints (Section 8.1.3.3). Central reading to be performed (Pettersson score). #Authorized time window to complete the X-ray at W156 is ±2 months
α-fetoprotein (CL)	X	X	X	X	X	To be tested as biomarker for hepatic carcinoma.
FVIII inhibitor testing (CL, test in LL if clinically necessary)	X	X	X	X	X	Samples should be collected in the absence of residual infused FVIII product (recommended washout is 72 h for standard half-life FVIII products and 120 h for standard and extended half-life FVIII products).

Procedures **Year 2 to Year 5**	**Week 53-104 (± 2 weeks)**		**Week 105-208- (± 3 weeks)**		**EOS or Early Discontinuation Week 260 (± 3 weeks)**	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Study Visit	14	15	16	17	18	
Weeks after study intervention	78	104	156	208	260	
						Nijmegen Bethesda Inhibitor Assay: to be done at the central laboratory unless testing at a local laboratory is necessary due to a clinical concern.
Neutralizing antibodies to AAV6 and other AAVs (CL)		X	X	X	X	Collect blood for serum preparation. nAb against other AAVs serotypes may be tested on same sample to assess cross reactivity.
Anti-drug antibody (CL)		X	X	X	X	Anti-PF-07055480 antibodies. Collect blood for serum preparation.
Laboratory safety panels: hematology and clinical chemistry (CL)	X	X	X	X	X	See Appendix 2 for a full list.
FVIII activity (CL, LL), LFT (CL, LL) and FVIII antigen (CL)	Starting at Week 53 and until week 156 (ie, during Year 2 and Year 3), monitor once every 3 months[#]: Weeks 65, 78 (Visit 14), 91, 104 (Visit 15), 117, 130, 143, 156 (Visit 16)		From Week 157, every 6 months [#]: Weeks 182, 208 (Visit 17), and 234		X[#]	• LFT: See Appendix 2 for a full list. • **FVIII activity and LFT testing will be conducted at local <u>and</u> central laboratories.** • **Any unscheduled or repeated blood testing for LFTs and/or FVIII activity must be conducted at local AND central labs.** • FVIII activity should be collected in the absence of residual infused FVIII product (recommended wash-out is 72 h for standard half-life FVIII products and 120 h for extended half-life FVIII products). • FVIII activity should be measured in the event of an untreated bleed, as close to the bleeding event as possible. If the bleed necessitates exogenous FVIII, FVIII activity should be assessed post clearance of FVIII product. See also Section 8.1.2. • It is recommended to repeat FVIII activity assessment anytime if there is a significant decrease (not attributed to standard fluctuation or to variability of assays) as assessed by the investigator. The medical monitor may be consulted as

Procedures **Year 2 to Year 5**	**Week 53-104 (± 2 weeks)**		**Week 105-208- (± 3 weeks)**		**EOS or Early Discontinuation Week 260 (± 3 weeks)**	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Study Visit	14	15	16	17	18	
Weeks after study intervention	78	104	156	208	260	
						needed. See also Section 8.1.2. Sponsor recommends collecting specimens on Monday through Thursday so results are available before the weekend. • FVIII antigen testing will be conducted ONLY at central lab. • Clinical decisions may be based on local and/or central lab results. • #Samples should be taken at Weeks 65, 78 (Visit 14), 91, 104 (Visit 15), 117, 130, 143, 156 (Visit 16), 182, 208 (Visit 17), 234, 260 (Visit 18). • Use home health/mobile phlebotomy services as needed. Refer to Section 8.3.10 for more guidance about elevated liver enzymes and/or optimization of immunomodulation.Note: if corticosteroid therapy is started, measurement of LFTs and of FVIII activity is recommended at least 2 times per week until the end of this therapy. • It is highly recommended that participants who are initiated on corticosteroid treatment be treated with a gastric acid reducer, preferably a proton pump inhibitor (PPI) (eg, omeprazole), or alternatively a histamine type 2 (H2) antagonist (eg, famotidine) for the duration of the corticosteroid course. • FVIII recovery may be tested if prophylaxis is resumed and/or if prophylaxis is administered prior to a surgical procedure. Refer to Section 8.1.2 for more guidance.
Immunology/ELISPOT (PBMC) (CL)	Only if corticosteroid treatment is needed for a suspected T-cell response. Home health/mobile phlebotomy services allowed.					• Collect specimens for PBMC preparation and ELISPOT if the corticosteroid treatment is needed for a suspected T-cell response. • Collect specimens before initiating the corticosteroid treatment. If specimens are not collected before initiation, then collect specimens within 24 hours of administering corticosteroids. • Collect specimens approximately 3 weeks after steroid administration and at the end of the weaning time. Additional specimens may be recommended by the sponsor, in consultation with the investigator, depending on the participant's response to corticosteroid therapy.

Procedures Year 2 to Year 5	Week 53-104 (± 2 weeks)		Week 105-208- (± 3 weeks)		EOS or Early Discontinuation Week 260 (± 3 weeks)	
Study Visit	14	15	16	17	18	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Weeks after study intervention	78	104	156	208	260	
Spare plasma	X	X	X	X	X	Draw approximately 5 mL of blood to prepare approximately 2 mL of plasma at each timepoint (when central analyses are done and at least, at each mandatory onsite visit and at each laboratory visit for ALT / FVIII assessment from Week 32 and until the End of Study Visit). Plasma will be stored for repeat or additional testing (including exploratory biomarkers to assess immune response and study intervention mechanism of action) (Section 8.10.3 and Section 8.10.4).
Liver ultrasound		X	X	X	X	All participants will undergo liver ultrasounds yearly, at a minimum, with more frequent ultrasounds allowed per investigator discretion (eg, participants with risk factors for HCC) or if necessitated to align with participant's standard of care. Refer to Section 8.2.4 and to the liver ultrasound scanning guidance. Authorized time window for liver ultrasound during the long-term follow-up period: ±1 month at W104 and ±2 months at W156 and W208. If the ultrasound cannot be performed at a visit, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.
Global hemostasis markers and thrombophilia related markers (CL)		X*	X*	X*	X*	• See Appendix 2 for a full list of possible markers and Section 8.2.8for more information. • These samples should be collected in the absence of residual infused FVIII product (recommended washout is 72 h for standard half-life FVIII products and 120 h for extended half-life FVIII products). • *Defined thrombophilia-related markers should be assessed at least once in each participant (if not initially assessed as part of eligibility confirmation) and some parameters can be repeated as clinically indicated, but are not repeated at each visit. • Hemostasis markers should be assessed as clinically indicated throughout the study and are recommended to be tested if vector-derived FVIII:C >150% of normal are achieved .
HJHS		X	X	X	X	To be completed by the investigator or the designee (Section 8.1.3.1). Authorized time window: ±1 month at W104 and ±2 months at W156 and W208.

Procedures **Year 2 to Year 5**	**Week 53-104 (± 2 weeks)**		**Week 105-208- (± 3 weeks)**		**EOS or Early Discontinuation Week 260 (± 3 weeks)**	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Study Visit	14	15	16	17	18	
Weeks after study intervention	78	104	156	208	260	
						If the HJHS cannot be performed at a visit, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.
PROs		X	X	X	X	Participants will complete 6 instruments at the study site using an electronic tablet: Haem-A-QoL, HAL (v2), HLIQ, EQ-5D-5L, PGIS (n=3), PGIC (n=3). Administer the questionnaires before dosing, treatment, or conversation between the health care team and participants about their health condition. See Section 8.1.4 for additional considerations. If PROs cannot be performed at a visit, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.
Phone call			Ongoing			After Week 156, phone calls every 6 months (ie, Weeks 182 and 234) in addition to the annual visits. Inquire about AEs and concomitant treatments (including surgeries).
Vector shedding analysis by PCR and infectivity (CL)	Every 2 weeks [#] Home health/mobile phlebotomy services allowed. From Week 34, monthly collection is allowed in the absence of home health/mobile phlebotomy services at a site or country					• [#]Collect plasma, PBMC, saliva, semen, and urine specimens every 2 weeks until 3 consecutive negative test results for the given specimen type. • Semen samples can be collected at home the night before a clinic or home health/mobile phlebotomy services visit and stored in the participant's freezer until the clinic or home health/mobile phlebotomy services visit. • Infectivity will be performed as applicable. Refer to Section 8.5.1 for additional details.
Any additional safety tests	Ongoing					Additional laboratory testing or procedures may be conducted as deemed clinically necessary by the investigator to ensure safety of participants.
Adverse events	Ongoing (including unscheduled visits)					During the short-term monitoring period (up to and including 104 weeks postinfusion) all SAEs and AEs will be collected (Section 8.3.1 and Appendix 3). During the long-term monitoring period (Week 105 postinfusion to EOS) the following adverse events will be collected: • SAEs (including medically important events, Appendix 3).

Procedures **Year 2 to Year 5**	**Week 53-104 (± 2 weeks)**		**Week 105-208- (± 3 weeks)**		**EOS or Early Discontinuation Week 260 (± 3 weeks)**	○ **Home health/mobile phlebotomy services may be used as needed** (for most biological samples collection only). ○ Clinical decisions may be based on **local or central laboratory** assessments**.**
Study Visit	14	15	16	17	18	
Weeks after study intervention	78	104	156	208	260	
						• Nonserious AEs determined to be related to study intervention by the investigator or where causality is unknown. Particular attention will be given to renal disease, autoimmune, neurological and hematological changes.
Concomitant medications and procedures	Ongoing (including unscheduled visits)					Record concomitant therapy (related to reportable events) through the EOS (see Section 6.5). All procedures and surgeries (including elective surgeries) will be recorded. Note: FVIII product infusions will be recorded in the eDiary.
Review of the eDiary	Ongoing (including unscheduled visits)					Review the eDiary and ensure appropriate entries during unscheduled and scheduled visits.
Return eDiary					X	The eDiary will be returned during the Week 260 visit.
Optional Liver Biopsy	X					Participants who consent to participate in this optional substudy will undergo liver biopsy. The biopsy may be performed at any time postinfusion when deemed appropriate by the investigator, and according to Section 8.2.8.

2. INTRODUCTION

2.1. Study Rationale

Sangamo Therapeutics has developed SB-525 (hereafter PF-07055480), an rAAV6 capsid and cDNA encoding for the BDD hFVIII. It encodes a liver-specific promoter module and rAAV6 exhibits liver tropism, thus providing the potential for sustained hepatic production of FVIII in hemophilia A participants to reduce or eliminate the need for FVIII replacement therapy.

PF-07055480 is being evaluated in an open-label, adaptive, dose-ranging Phase 1/2 study (SB-525-1603 [hereafter C3731001]) to assess the safety and tolerability in male participants ≥18 years of age with severe hemophilia A. The preliminary data from the Phase 1/2 study indicate that treatment of hemophilia A with PF-07055480 offers clinical advantage over routine prophylactic treatment with FVIII. Specifically, these data indicate that treatment of hemophilia A with PF-07055480 is well tolerated and demonstrated a dose-dependent increase in FVIII levels, achieving clinically relevant increases in FVIII activity in the higher dose cohorts and at or near normal FVIII levels in the 3×10^{13} vg/kg highest dose cohort (normal range: 50-150%). In the highest dose cohort, participants did not require factor replacement therapy (after initial use of prophylactic factor) and experienced no bleeding events in the first year post dosing.

The Phase 3 program includes 2 separate studies: a non-IMP lead-in study (C0371004), where data will be prospectively collected in the context of routine prophylaxis with FVIII products, and this C3731003 pivotal Phase 3 dosing study.

C3731003 pivotal Phase 3 study will further evaluate the clinical efficacy and safety of PF-07055480 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). 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 primary analysis will be conducted when at least 50 dosed participants with 6 months of follow up in the Lead_In study (C0371004) have reached at least 15 months of follow-up postinfusion (ie, data cutoff for primary analysis), 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 (ie, approximately 3 months) for the primary analysis.

The primary endpoint in this study (C3731003) will be the Total ABR, including both treated and untreated bleeding events, and it will be compared with prior routine prophylaxis. The Total ABR will be assessed from Week 12 through at least 15 months postinfusion up to data cutoff.

FVIII activity level >5% at 15 months postinfusion will be a key secondary endpoint.

The other key secondary endpoint is the ABR (treated bleeding events) from Week 12 through at least 15 months postinfusion up to data cutoff, compared to preinfusion prophylaxis.

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

2.2. Background

PF-07055480 (SB-525)

Gene therapy approaches in hemophilia A have been historically constrained by the large size of hFVIII gene, the high AAV dose required to achieve therapeutic FVIII levels, and the low manufacturing yields of AAV hFVIII. PF-07055480 has a shorter coding sequence for hFVIII 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.

2.2.1. Summary of Clinical Experience with PF-07055480

Eleven (11) participants have been treated across 4 escalating dosage cohorts in the Phase 1/2 study with 2 participants each in Cohorts 1 to 3 (9×10^{11} vg/kg, 2×10^{12} vg/kg, and 1×10^{13} vg/kg, respectively) and 5 participants in Cohort 4 at the Phase 3 dose of 3×10^{13} vg/kg.

Participants demonstrated a nonlinear dose-related increase in FVIII activity levels, achieving clinically relevant increases in FVIII activity in the higher dosage cohorts and at or near normal FVIII levels in the 3×10^{13} vg/kg dose cohort (normal range: 50 -150%) by the chromogenic substrate assay.

In the highest dose cohort, participants did not require factor replacement therapy (after initial use of prophylactic factor) and experienced no bleeding events in the first year post dosing.

The most common treatment-related AEs in Cohort 4 were ALT and AST elevation, fever, and tachycardia. The respective episodes of fever (3 participants in Cohort 4) and the respective episodes of tachycardia (2 participants in Cohort 4) were Grade 1 or 2 in severity;

all episodes occurred within a day of dosing of PF-07055480. ALT and AST elevations were all of Grade 1 (3/4 participants) or 2 (1/4 participant) in intensity. Onset of ALT elevations occurred between 4 to 12 weeks after dosing and all resolved following tapering courses of corticosteroids. In all instances, corticosteroid taper was initiated within 12 weeks of corticosteroid implementation.

A treatment-related serious adverse event was reported in 1 participant at the 3 x 10^{13} vg/kg dose level (Cohort 4) and consisted of severe hypotension (Grade 3) and fever (Grade 2), with an onset 6 hours after completion of PF-07055480 infusion. The participant was treated with PPD and was discharged 24 hours after the end of the PF-07055480 infusion, with no clinical signs remaining. Four other participants have subsequently been dosed at the 3 x 10^{13} vg/kg dose level and overall treatment was well tolerated with no other occurrence of Grade 3 or higher treatment related AEs. Allergic reactions, which may include hypotension and fever, were previously identified as potential risks of treatment with PF-07055480 and an Infusion Reaction Management Guide (with premedications and follow-up recommendations) will be implemented in this Phase 3 study.

No participants experienced AEs leading to discontinuation of study participation and there was no emergence of confirmed FVIII inhibitors.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-07055480 may be found in the Investigator's Brochure, which is the single reference safety document for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Identified Risks Associated with the Study Intervention		
Infusion reactions (including hypersensitivity)	PF-07055480 may induce infusion-related reactions (IRRs) during or following administration. These reactions may be due to immune reactions and/or allergic reactions/hypersensitivity and lead to fever, chills, tachycardia, headache, nausea, vomiting or hypotension. Several complex processes contribute to generating an immune response against an offending pathogen. Because AAV vectors lack any coding viral sequence, the main sources of foreign antigens brought in during gene transfer, aside from contaminant carryovers from the production and purification process, include the viral capsid.[1] Innate immunity mounts rapidly, is non-specific, and does not result in immunological memory. In the C3731001 Phase 1/2 study, IRR symptoms that occurred within a day of infusion included fever, tachycardia and hypotension. A case of severe hypotension occurred in one participant treated at the 3 x 10^{13} vg/kg dose which is being studied in this study, 6 hours after the end of the infusion and was successfully treated with PPD with discharge within 24 hours after the end of the study drug infusion.	To minimize and manage a potential adverse immune response to PF-07055480 or its excipients, premedication with acetaminophen and/or diphenhydramine hydrochloride is recommended before initiating dosing and during infusion. In addition, IV infusion will occur while the participant is in the hospital or acute care facility, where he will remain for observation for a sufficient period of time postinfusion (at least 24 hours), to monitor for an acute reaction and ensure the participant is in stable condition prior to discharge. An IRR management guide which provides recommendations (summarized in the IB Section 7.4.1 [Infusion Reactions [Including Hypersensitivity]]) on the infusion practice and clinical management of the study participants before, during and after PF-07055480 infusion (until discharge) will be distributed to the clinical sites.
Potential Risks Associated with the Study Intervention		
Hepatotoxicity	The potential risk of liver inflammation for this liver-tropic viral vector is due to the activation of the immune system in the liver. All mechanisms are not elucidated but the T-cell mediated immune response activation may play a key role.[2] The vector capsid remains behind in the cytosol of the transduced hepatocyte and undergoes proteasomal processing. Capsid-derived peptides are then transported to the endoplasmic reticulum and loaded onto MHC I molecules. CD8+ T-cells may recognize the viral vector capsid proteins which are presented as peptides on the surface of transfected hepatocytes that take up the rAAV. This may lead to transduced liver cells being killed by cytotoxic T lymphocytes and ultimately, to FVIII activity decrease. Activation of CD8+ T-cells	Participants with markers of hepatic inflammation, cirrhosis, or fibrosis beyond limits specified in the protocol will be excluded from participation in this study, and hepatotoxic concomitant medications should be avoided. Routine corticosteroid prophylaxis is not planned. However, due to a lack of clear predictability of a liver response based on NHP studies and the possibility of decreased gene expression when corticosteroid initiation is delayed, both liver function tests and FVIII activity levels will be closely followed during the study (with frequent

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	and presentation of capsid-derived peptides must occur in a similar time course to result in a clinically detectable event. Liver inflammation can be detected by elevated blood liver enzymes (transaminases; ALT and/or AST). No published preclinical study in non-human primates (NHP) of any of AAV vectors showed a predictable liver response.[3,4,5,6] All clinical studies reported thus far using AAV in hemophilia have shown a similar pattern where liver effects are seen approximately 3 to 10 weeks (depending on the serotype and possibly on vector dose) after administration. ALT elevations are often accompanied by a decrease in transgene expression. ALT usually normalizes within a few weeks of initiating corticosteroids; however, a loss of transgene expression, when observed, did not typically recover. In the ongoing Phase 1/2 (C3731001), all transitory elevations of liver function tests (LFTs) have been successfully treated with corticosteroid.	measurements as specified in the Schedule of Activities [Section 1.3]) and corticosteroids will be administered at the first sign of liver inflammation. If there is evidence of transaminitis, the dose of prednisone or equivalent corticosteroid will be initiated as specified in Section 8.3.10 (Immunomodulation Optimization [Presumed T-Cell Activation]) of this study protocol. At this point, liver function and FVIII activity will be assessed twice a week until normalization of liver enzymes, and then per protocol thereafter. In addition, T-cell response will be assessed by a specific assay (ELISPOT) until normalization.
Neutralizing antibodies to AAV6	Administration of AAV vectors leads to the production of a humoral immune response to AAV. In clinical trials to date, anti-AAV neutralizing antibodies have been detected in all participants after vector infusion.[1] The presence of neutralizing antibodies to AAV prior to PF-07055480 administration can affect transduction by forming immune complexes with the infused vector, and thereby prevent hepatocyte transduction.	Prior to the administration of PF-07055480, participants will be screened for neutralizing antibodies to AAV6 and those testing positive at the pre-specified threshold will not be administered PF-07055480. In general, antibodies against PF-07055480 (total and neutralizing) will be continuously assessed throughout this study.
FVIII inhibitors	Factor VIII inhibitors are antibodies to FVIII that neutralize the clotting activity of FVIII. Development of inhibitors to administered FVIII is a known complication in 25-30% of severe hemophilia A patients. Influences for developing inhibitors include FVIII mutations, human leukocyte antigen (HLA) associations, and type of factor treatment (plasma derived factor concentrates or recombinant).[7] Potential risk factors are early intensive replacement therapy and source of FVIII (human plasma or recombinant).[8,9] In theory, there is a possibility that inhibitors to FVIII transgene can also develop. However, in the context of AAV trials, anti-transgene immune responses have been documented in only a few instances, mostly in the context of intramuscular delivery of AAV vectors.	Participants with prior history of FVIII inhibitor (clinical or laboratory-based assessment) will be excluded from this study. Participants will also be required to have at least 150 documented EDs to a FVIII protein product (standard half-life or extended half-life recombinant, plasma derived) to be eligible for the study. This reduces the risk of inhibitor development as nearly all inhibitors occur prior to 50 EDs. Study participants will also be assessed for the development of FVIII inhibitors at routine intervals post-PF-07055480 infusion, as described in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Indeed, one key factor determining the level of antitransgene immune responses is the target organ for gene transfer, which is determined by the combination of the AAV capsid, the vector delivery route, and the tissue specificity of the promoter driving gene expression. In particular, systemic and intramuscular vector administration, with either ubiquitous or muscle-specific promoters, have been shown to be more immunogenic than gene transfer to immune privileged organs as liver, as well as systemic administration with liver-specific promoters.[1] In addition, high titer inhibitors generally do not occur after 150 exposure days[10] but may encounter a second peak in participants older than 60.[11] Current AAV clinical trials in previously treated participants include participants with >150 exposure days (EDs) and no evidence of an inhibitor prior to entering a trial for a novel FVIII investigational product.[6] To date, none of the participants enrolled in the AAV hemophilia trials have developed inhibitors.[12] In addition, none of the 11 participants dosed with PF-07055480 in the ongoing Phase 1/2 Study C3731001 have developed confirmed FVIII inhibitors.	protocol. There are existing protocols of treatment for patients with inhibitors such as use of the hemostatic bypass to treat or prevent bleeding and repeated infusions of FVIII to induce immune tolerance and reduce inhibitor levels.[13] This study may be paused in the event of a confirmed inhibitor level for a participant; no additional participant will be treated until the circumstances for such an event are assessed and regulatory agencies are notified, if required.
Thromboembolic events	Some participants in the Phase 1/2 Study C3731001 and in this Phase 3 study experienced FVIII activity levels >ULN. To date, no events of thrombosis or evidence of excessive coagulation have been reported in the ongoing Phase 1/2 Study C3731001. One event of thrombosis was reported to date (DVT) in this ongoing Phase 3 Study C3731003; it occurred in a participant who had multiple risk factors, PPD	Hemostasis parameters including, but not limited to, D-Dimer and thrombin-antithrombin levels as thrombotic potential will be measured on a regular basis and if vector-derived FVIII:C activity levels are >ULN in any participant during this study. In addition to activity levels, expression of FVIII antigen and of von Willebrand factor will also be regularly monitored. Participants will be monitored for any signs of adverse events. Investigators will be provided with a guidance to manage participants with FVIII activity levels >ULN ("Management Guide for Elevated Factor VIII Activity Levels"), summarized in Section 8.1.2 (Factor VIII activity) and in Section 8.2.7 (Hemostasis Parameters and Thrombotic Potential Assessment).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Participants with conditions associated with increased thromboembolic risk such as inherited or acquired thrombophilia, or a history of thrombotic events, including but not limited to stroke, myocardial infarction, or venous thromboembolism, are excluded. This study will be paused in the case of an initial thrombotic event suspected to be related to >ULN FVIII activity levels for a participant; no additional participant will be treated until the circumstances for such an event are assessed and regulatory agencies are notified, if required. In the case of recurrence of a thrombotic event in a participant, the DMC will be convened urgently to assess the event. DMC recommendations will be taken into account in the decision to pause the study.
Off target effects	Transgene expression is driven by an expression cassette that contains a human liver-specific promoter. This restricts hF8 expression to the liver as confirmed both in mice and NHPs where FVIII messenger ribonucleic acid (mRNA) expression was not detected in heart tissue. Recombinant AAV6 hFVIII vector genomes were detectable in other tissues (eg, heart), at levels several orders of magnitude lower than found in the liver and are not anticipated to present a clinical risk. However, there is the potential for capsid antigen presentation in the heart, should a cardiomyocyte be transduced by PF-07055480, and consequently the potential for a T cell response to occur. To confirm that rAAV6 vector genomes produce no damage to heart muscle, electrocardiograms (ECGs) were performed at baseline and yearly postinfusion in the ongoing Phase 1/2 Study C3731001. To date, no clinically significant ECG abnormalities have been detected.	In this study, to monitor for such an event, baseline Troponin I will be measured at several time points in the first 18 weeks post-dosing, and in addition, if elevations in transaminases are observed that could signal a potential T-cell response to capsid antigen, then Troponin I will also be evaluated. If a confirmed elevation in Troponin I is observed greater than 99th percentile for upper limit of normal (ULN) confidence interval (CI), an ECG will be performed, and a cardiologist consulted. In addition, ECGs will be performed at baseline and annually.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Insertional mutagenesis	Following cellular transduction by AAV, most transgenes remain extrachromosomal as an episome; however, a small proportion have been found to integrate into the genome of transduced cells.[14,15,16,17] Data from mice, dogs, NHPs and humans suggest that the integration of AAV vectors is a rare event, with most of the vector assimilating into concatemeric episomes.[18,19,20] Unlike retroviral vectors, which encode viral proteins to create double-stranded breaks, when AAV integration does occur, it does so at preexisting chromosomal breaks.[19,21] The results of integration are deletions in the AAV inverted terminal repeats (ITRs) and duplications of host sequences. Given the tissue tropism of AAV6 and the results of non-clinical and clinical studies, the greatest potential for integration is within hepatocytes and to a much lesser extent in skeletal and cardiac myocytes (recombinant AAV2/6 hF8 vector genomes were detectable in other tissues (eg heart), but levels were several orders of magnitude lower than found in the liver). The mouse and monkey studies performed with PF-07055480 showed no findings of tumors by gross and histopathologic examination.[16] Although there is no adequate animal model to address the tumorigenic potential, the available data from toxicology studies did not show any tumor formation. In the ongoing Phase 1/2 Study C3731001, no neoplastic events, abnormal alpha-fetoprotein (AFP) and/or liver masses have been observed to date.	The choice of AAV as the basis for PF07055480 already lowers the risk significantly. Participants in this study will be observed for at least 5 years post-dosing. In this study, for evaluation of liver carcinogenicity, hepato-cellular carcinoma (HCC) screening and monitoring will be conducted, which includes liver ultrasound and blood AFP measurements (blood marker of hepatocarcinoma) performed at least on an annual basis during the 5-year study duration. Liver biopsy is recommended if there is an abnormal AFP and a >2 cm mass in the liver.[22] Vector integration will be assessed on all available liver samples (collected to further assess abnormalities and/or via the optional liver biopsy substudy).
Germ line transmission from treated patients to the general population via transduction of germ cells or transmission of vector in sperm	Non-clinical studies in rabbits and human clinical studies indicate that AAV2 and AAV8 vectors shed to body fluids, including semen. In rabbits, the duration of detection of vector genomes in the semen is dose-dependent and time-dependent, with AAV infectious particles present up to Day 4 post-injection and undetectable thereafter.[23] The virus present in these samples are in the seminal fluid, but transduction of sperm cells does not occur even at doses of AAV that are orders of magnitude above what is found in seminal fluid.[24] This is consistent with the findings of several studies in rabbit and mouse suggesting that the risk of inadvertent germline transmission in males following IV administration of AAV vectors	This study will enroll male participants only. Participants in this study will be required to refrain from donating sperm, be abstinent (and agree to remain abstinent) or wear condoms during sexual activities until the vector can no longer be detected 3 consecutive times in a row in semen.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	is negligible. Transduction of spermatocytes or sperm cells has not been observed yet.[23,24,25,26,27,28] No data are available suggesting transmission of the AAV vector to the offspring of an exposed male participant.	
Spread of vector from treated patients to other humans/organisms/environment	PF-07055480 theoretically may be transmitted to persons other than a participant in this study. The recombinant vector is replication-incompetent and is not expected to survive, multiply or disperse if it were to be eliminated intact from a treated patient. Recombinant AAV vectors have been substantially modified compared to wildtype AAV. PF-07055480 is replication defective due to removal of all the viral gene coding sequences, including the rep and cap genes, required for replication. As a consequence, PF-07055480 is replication defective even in a cell co-infected with known AAV helper viruses (adenovirus, herpesvirus). Following injection into the patient, PF-07055480 replication could only occur in the extremely unlikely event of a host cell being coinfected by three separate entities (PF-07055480, wild-type AAV and a helper virus such as human adenovirus or herpes simplex virus). In the ongoing Phase 1/2 Study C3731001, vector shedding has been assessed using quantitative real-time PCR (qPCR) analysis of saliva, urine, semen, stool, and plasma. Data suggested that that the levels of shedding vector were generally highest during the first couple of weeks after vector infusion, and gradually declined in all types of specimens.	Vector shedding will be monitored and will be measured by quantitative PCR in plasma, peripheral blood mononuclear cells (PBMC), saliva, semen and urine of participants following administration of PF-07055480 until 3 consecutive samples, for each matrix tested, demonstrate a qPCR signal at or below the limit of assay detection. Should intact vector particles be shed into the environment, these particles will still be non-replicative and nonpathogenic. Vector particles would be degraded quickly in the environment. Hence, the chance of harm being caused by spread of the vector in the environment is negligible. Participants in this study will be required to refrain from donating sperm, be abstinent (and agree to remain abstinent) or wear condoms during sexual activities until the vector can no longer be detected 3 consecutive times in a row in semen.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Risk Associated With the Study Procedures		
Placement/Removal of an IV catheter	The placement of an IV catheter and bleeding after removal of the catheter are both considered low risk. With any parenteral injection, a risk of local or systemic infection also exists.	In this study, bleeding risk will be lowered by the application of local pressure according to the standard procedure following IV infusions. In addition, it is recommended that participants receive an infusion of FVIII replacement therapy within 24 hours prior to the PF-07055480 infusion, as indicated in the protocol, and will have appropriate factor coverage for approximately 2 weeks post PF-07055480 infusion. In order to minimize the risk of infection, PF-07055480 will also be administered using standard sterile techniques.
Optional liver biopsy	The procedure of percutaneous liver biopsy and inserted needle can lead to bleeding and perforation to nearby organs (with serious complications occurring less than once in every 10,000 procedures). A risk of local or systemic infection also exists.	To reduce these risks, a robust pre- and post-biopsy surveillance plan according to the local procedures and as suggested in Section 8.2.8 is recommended. It is recommended that participants have a FVIII activity level of ≥ 50% (or higher, depending on local guidelines and/or investigator discretion) when doing the procedure. In order to minimize the risk of infection, standard sterile techniques will be used.

2.3.2. Benefit Assessment

The major benefit of gene therapy is that it may provide persistent treatment of hemophilia by continuous endogenous production of functional FVIII, providing therapeutic effect and a relief from the medical and lifestyle burden of recurrent on demand or routine prophylactic protein replacement therapy. By providing a stable production of serum FVIII levels, protection for bleeding episodes may be provided. Although replacement therapy increases FVIII levels in the bloodstream, these levels include peaks and troughs that are non physiological and lead to less protection before the next infusion. Gene therapy may also favourably impact the recognised complications of hemophilia: recurrent hemarthroses and the subsequent arthropathy. It is feasible that gene therapy treatment may result in expression of FVIII consistent with conversion from a moderate or severe to a mild hemophilia or better, persisting for at least a decade.[19,29] Under such circumstances, treatment could offer a major contribution to patient care whereby sufferers of hemophilia A could be considered largely relieved of disease symptoms and the burden of treatment. Gene therapy may also be especially beneficial to individuals that have difficulty maintaining adequate adherence to the regular prophylaxis treatment whether due to lack of compliance, the burden of care imposed by prophylactic treatment regimens or other considerations such as lack of sufficient venous access.

Phase 1/2 study provided preliminary evidence of PF-07055480 efficacy in terms of FVIII activity with associated decreases in bleeding episodes, FVIII consumption and replacement infusions. The aim of this Phase 3 study is to further assess these potential clinical benefits after infusion of study intervention. Additional benefits of study participation include close medical monitoring during the study including where appropriate, but not limited to physical exams, ECGs and liver ultrasounds.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with PF-07055480 are justified by the anticipated benefits that may be afforded to participants with hemophilia A.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints
Primary Efficacy Objective	**Primary Endpoint and Key Secondary Endpoints**
• 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 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.

Objectives	Endpoints
	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.	• 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 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 compared with prior FVIII prophylaxis replacement regimen: • Annualized FVIII consumption. • 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 HJHS instrument.

Objectives	Endpoints
	• Change from baseline in the following PRO endpoints: • Haem-A-QoL • 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: • ABR. • FVIII activity level. • AIR of exogenous FVIII. • Annualized FVIII consumption. • ABR of specific type: o by cause (spontaneous or traumatic). o 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, 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 AEs. • Events of special interest (such as hypersensitivity reactions, clinically

Objectives	Endpoints
	reported thrombotic events, and malignancy). • Immunogenicity: o Antibodies against AAV6 capsid protein (nAbs and ADAs). o T-cell responses against AAV6 capsid and against the transgene. o FVIII inhibitors.
Tertiary/Exploratory	
• To evaluate vector shedding and infectivity in body fluids.	• Vector shedding and infectivity of PF-07055480 in plasma, saliva, PBMC, urine, and semen until negative on 3 consecutive occasions for each specimen type.
• 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: aPTT, INR, D-dimer, TGA, and 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: • HLIQ

Objectives	Endpoints
	• EQ-5D-5L
• To further evaluate PF-07055480 mechanism of action and immune responses.	• Cellular immunity by cell-mediated assays. • Binding IgG versus 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 • To evaluate the histopathology of the liver tissue • To assess the expression of protein and/or RNA levels of FVIII and other biomarkers of interest in the liver	• For the integrations analyses (as feasible): the number and location of integration sites, the location of the integration sites relative to transcription start sites, the nature of the inserted sequence, the frequency of insertions, and the frequency and distribution for each size and type of insertion • Other exploratory endpoints (as feasible): histopathology assessment (eg. presence of fibrosis assessment, presence of lymphocytic invasion), protein and/or RNA expression of FVIII and selected biomarkers (eg. Grp78, Gal3BP)

The primary estimand is the treatment effect of PF-07055480 with respect to Total ABR (including both treated and untreated bleeding events) after the estimated FVIII activity steady state onset, ie, from Week 12 through at least 15 months postinfusion or until resumption of FVIII prophylaxis regimen (if necessary). Total ABR will be analyzed using comparisons of postinfusion PF-07055480 Total ABR versus preinfusion Total ABR collected during the lead-in study (C0371004) and prior to dosing in this study (C3731003) using a repeated measures negative binomial regression model. Data before Week 12 postinfusion are excluded to account for the potential differences in participants' pharmacokinetics post infusion. Data following resumption of the prophylaxis FVIII regimen (if necessary) will be excluded. Because no more than a single dose of study intervention will be administered during the study, there should be no treatment discontinuations.

The secondary estimands are the treatment effect of PF-07055480 with respect to FVIII activity level >5% at 15 months postinfusion and the ABR (treated bleeding events) from Week 12 through at least 15 months postinfusion.

Any sample taken within 72 hours of standard half-life exogenous FVIII replacement therapy or 120 hours of extended half-life exogenous FVIII replacement therapy

administered for any purpose (including treatment of bleeding or prevention purposes) will be excluded from the assessment of FVIII activity level at 15 months. Additionally, any FVIII activity levels after the resumption of FVIII prophylaxis regimen before 15 months will be replaced with 0.9% for analysis purposes, and therefore considered as having FVIII activity ≤ 5%. Because no more than a single dose of study intervention will be administered during the study, there should be no treatment discontinuations. Missing data are anticipated to be rare; thus, there will be no imputations for missing data.

ABR will be analyzed using the same analysis method as described for Total ABR.

4. STUDY DESIGN

4.1. Overall 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 a 6-week screening and baseline period followed by the dosing day (Day 1), a 2-year efficacy and safety observation period (short term follow-up), and a 3-year long-term follow-up period. After this 5-year follow-up period in Study C3731003, participants will be invited to enter a separate study to assess the long-term safety and effectiveness of PF-07055480 for the treatment of hemophilia A and to allow follow-up for a total of up to 10 additional years post-study, corresponding to up to 15 years post-PF-07055480 infusion. This long-term follow-up study is planned to assess the durability of efficacy demonstrated through main efficacy endpoints of FVIII activity levels, the occurrence of bleed events (eg, ABR) and FVIII product use. The safety follow-up is planned to include the collection of SAEs, AEs of special interest (eg, hypersensitivity reactions, thromboembolic events, liver abnormalities, FVIII inhibitor, malignancy, cardiovascular events) and all-cause mortality. Visits are planned to occur as per standard practice for each site to include at least 1 annual visit.

Approximately 70 participants from the lead-in Study C0371004 will be enrolled and eligible participants will be assigned to study intervention to achieve a desired sample size of at least 50 dosed participants completing at least 15 months of follow-up postinfusion. These 50 participants will have completed at least 6 months of routine prophylaxis follow-up in Study C0371004.

The primary analysis will be conducted when at least 50 dosed participants with 6 months of follow up in the Lead In study (C0371004) have reached at least 15 months of follow-up postinfusion (ie, data cutoff for primary analysis), 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 (ie, approximately 3 months) for the primary analysis.

The primary analysis will assess the Total ABR, including both treated and untreated bleeding events, and it will be compared with prior routine prophylaxis. The Total ABR will be assessed from Week 12 through at least 15 months postinfusion up to data cutoff in at least 50 dosed participants (Figure 1), compared to preinfusion prophylaxis.

FVIII activity level >5% at 15 months postinfusion will be a key secondary endpoint. The other key secondary endpoint is the ABR (treated bleeding events) from Week 12 through at least 15 months postinfusion up to data cutoff in at least 50 dosed participants, compared to preinfusion prophylaxis.

The final analysis will be conducted when all dosed participants have completed the entire study (ie, 5 years of 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 >ULN FVIII activity levels for a participant as further described in Section 8.2.7.2 and in Section 8.1.2.3.

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.

4.2. Scientific Rationale for Study Design

Collecting prospective data in the lead-in study and collecting data after a single PF-07055480 infusion allows for comparison analyses and a relatively low number of participants for a statistically robust study. During this lead-in study, eligible adult participants would have received prophylaxis with FVIII replacement product as part of SOC along with on-demand infusions as necessary for bleeding events.

The planned study duration of 5 years for each participant takes into consideration the EMA and FDA Guidances for gene therapy[30,31,32,33] and includes 2 years of initial efficacy and safety observations (short-term follow-up) followed by a 3-year efficacy and safety long-term follow-up period. The short-term follow-up period focuses on efficacy and safety concerns expected within the first 2 years and will include frequent visits and laboratory assessments with special emphasis placed on liver, cardiac toxicity, inhibitors and FVIII

activity. During this period, all AEs and SAEs will be collected. Monitoring of liver function and FVIII activity will continue during the next 3 years of follow-up. In addition, other potential systemic complications (such as renal disease, autoimmune, neurological, or hematologic changes), medically important events, and events related to study intervention (or when causality is unknown) will be monitored.

The primary efficacy endpoint will be the Total ABR (including both treated and untreated bleeds) from Week 12 through at least 15 months following infusion of PF-07055480 in at least 50 dosed participants. The ABR (treated bleeds) from Week 12 through at least 15 months postinfusion will be a key secondary endpoint. Analyses will be based on comparisons of Total ABR and ABR before treatment with PF-07055480 (lead-in C0371004 study and preinfusion of PF-07055480 in this study [C3731003]) and following treatment with PF-07055480.

Annualized bleeding rate is an endpoint demonstrating meaningful clinical benefit that has been used as the primary endpoint in prelicensure studies of new FVIII and FIX products and is strongly associated with long-term joint function.[34]

FVIII activity level >5% at 15 months postinfusion will be another key secondary endpoint.

Factor VIII levels determine the severity of the disease and correlate with the risk of bleeding episodes.[35] In studies of prophylaxis in hemophilia A and in hemophilia B participants, higher doses of the respective clotting factor products administered at the same frequency as lower doses resulted in a lower incidence of bleeding episodes into joints and bleeding episodes, respectively.[36,37] The increase in FVIII activity reduces the ABR, and this reduction in the ABR (ie, treated bleeding episodes) has been used as the endpoint for assessing efficacy of FVIII prophylaxis treatment regimens. As FVIII gene therapy assures consistent expression of FVIII activity, clotting factor activity is also an accurate and objective endpoint to evaluate efficacy.[38]

FVIII activity at 15 months will be compared to a fixed threshold of 5% activity to determine the percentage of participants reaching this threshold. The therapeutic range of FVIII is wide and levels above 5% reflect a range of FVIII activity that is clinically meaningful based on reducing the frequency of bleeding episodes in general and the frequency of episodes of hemarthrosis, a major risk of hemophilic arthropathy.

4.3. Justification for Dose

The data from the Phase 1/2 study indicate that the single dose of 3×10^{13} vg/kg of body weight has an acceptable safety profile and is efficacious in all 5 participants with severe hemophilia A (<1%) treated at this dose (Section 2.2). All participants at this dose have had increases in FVIII activity and at or near FVIII levels within the normal range, with no bleeding episodes and FVIII product infusions reported in the first year post dosing.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed the entire study including EOS visit (Week 260).

The end of the study is defined as the date of the EOS visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:
Age:

1. Participant must be ≥18 and <65 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants must have been followed on routine FVIII prophylaxis therapy in the lead-in study (C0371004) and have ≥150 documented exposure days to a FVIII protein product (standard half-life or extended half-life recombinant, plasma derived).
3. Participants who have documented moderately severe to severe hemophilia A defined as circulating FVIII activity levels ≤1%.
4. Participants must agree to suspend prophylaxis therapy for hemophilia A after administration of the study intervention (see guidance in general notes of SoA). FVIII replacement therapy is allowed as needed (see Section 6.5.1).
5. Acceptable screening central laboratory values as follows:
    - Hemoglobin ≥11 g/dL
    - Platelets ≥100,000 cells/µL;
    - Creatinine ≤2.0 mg/dL.

Sex

6. Male

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male Participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time required for 3 consecutive ejaculate samples to test negative for vector shedding:

- Refrain from donating sperm.

PLUS, either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below.
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

For German sites, please refer to Country-Specific Appendix (Section 10.8.3).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Anti-AAV6 nAb titers, above or equal to the established threshold of 1:4, performed by a central laboratory during screening**.**
2. Prior history of FVIII inhibitor (clinical or laboratory-based assessment) defined as a titer ≥0.6 BU/mL, regardless of the laboratory normal range, or any measured Bethesda inhibitor titer greater than the ULN for the laboratory performing the assay. Clinically, no signs or symptoms of decreased response to FVIII administration.
3. Known hypersensitivity to FVIII replacement product or intravenous immunoglobulin administration.
4. History of chronic infection or other chronic disease that investigator deems an unacceptable risk. In addition, any participant with conditions associated with increased thromboembolic risk such as inherited or acquired thrombophilia, or a history of thrombotic events, including but not limited to stroke, myocardial infarction, or venous thromboembolism, is excluded.

5. Any concurrent clinically significant major disease or condition or other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior (including alcoholism) or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. In addition, any participant with a history of a neoplasm (including hepatic malignancy) that required treatment (eg, chemotherapy, radiotherapy, immunotherapy), is excluded, except for adequately treated basal or squamous cell carcinoma of the skin or a surgically removed benign neoplasm not requiring chemotherapy, radiotherapy and/or immunotherapy. Any other neoplasm that has been cured by resection should be discussed between the investigator and sponsor.
6. ALT, AST, ALP >2x ULN, based on central laboratory results.
7. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%), based on central laboratory results.
8. Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, hepatic encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones), is acceptable if the participant otherwise meets entry criteria.

Note: Participants who have a central laboratory test value that is outside the range specified by the exclusion criteria may have the test repeated, by the central laboratory, to determine eligibility; however, the result must be available prior to Baseline Visit/Visit 2.

Prior/Concomitant Therapy:

9. Currently on antiviral therapy for hepatitis B or C.
10. Any participant with a planned surgical procedure requiring FVIII surgical prophylactic factor treatment in the next 12 months.
11. Participants using therapies that are restricted. See Section 6.5.2 for therapies not allowed during study participation.
12. Participants who previously received PF-07055480 or any other gene therapy.

Prior/Concurrent Clinical Study Experience:

13. Previously dosed in a gene therapy research trial at any time or an interventional clinical study within the last 12 weeks, excluding participation in Study C0371004.

Diagnostic Assessments:

14. Active hepatitis B or C:
    - HBcAb, HBsAg, and HBV DNA positivity. Exception: if a participant is positive for HBcAb, then HBsAg and HBV DNA must be negative for inclusion.
    - HCV-RNA positivity.

15. Significant liver disease, defined by pre-existing diagnosis of portal hypertension, splenomegaly or hepatic encephalopathy. Additionally, during screening, a serum albumin level below normal limits and/or significant liver fibrosis by any of the following diagnostic modalities (Please note that only 1 test is needed for screening purposes): FibroScan score >8 kPa units, Fibro Test/FibroSURE >0.48. If there is concern regarding the FibroTest or the FibroScan results due to a confounding medical history (eg, proteinuria can impact FibroTest result), or in the event of conflicting results between the modalities, the investigator should contact the sponsor for further guidance.
    Note: if a participant has a known history of Gilbert's syndrome, a FibroTest cannot be used for fibrosis testing.
16. Serological evidence of HIV-1 or HIV-2 with either CD4+ cell count ≤200 mm^3 or viral load >20 copies/mL.

Other Exclusions:

17. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.
    For German sites, please refer to Country-Specific Appendix (Section 10.8.3).
18. Unable to comply with scheduled visits, infusion of PF-07055480 in the investigator's judgement.
    For German sites, please refer to Country-Specific Appendix (Section 10.8.3).
19. Unable or unwilling to comply with the protocol.
20. Sensitivity to heparin or heparin-induced thrombocytopenia.
21. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator or the sponsor's Medical Monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

1. Participants are expected to remain compliant with inclusion criterion 6 at least until 3 consecutive ejaculate samples test negative for vector shedding.
2. Participants should report increased alcohol consumption (compared to usual/baseline consumption).
3. Participants should be informed that alcohol consumption could contribute to abnormally elevated LFT results and thereby delay the infusion of the study drug. In addition, participants who report increased alcohol consumption (which is any amount of alcohol consumption greater than the baseline amount for that participant) at any time throughout the study, should have at a minimum local LFTs and FVIII activity monitored.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants are required to sign a new ICF and will be assigned a different participant number. Some procedures may need to be repeated based on the rescreening date, the protocol's screening/baseline authorized time windows and after consulting with the sponsor's medical monitor.

Participants who have a central laboratory test value that is outside the range specified by the exclusion criteria may have the test repeated, by the central laboratory, to determine eligibility; however, the result must be available prior to Baseline Visit/Visit 2.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Single arm study
Intervention Name	PF-07055480
Type	Gene therapy
Dosage Form	Injectable
Dose Strength	1.0×10^{13} vg/mL This nominal strength will be used for dosage calculation
Dosage	Single infusion: 3×10^{13} vector genomes/kg body weight. For a participant with BMI >30 kg/m^2, dose will be calculated based on an adjusted body weight determination that assumes a maximum permissible BMI of 30 kg/m^2, eg, for 187.96 cm (6'2") height and 167.8 kg weight (BMI 47.5 kg/m^2) dose will be based on 106.1 kg, which is the weight associated with a BMI of 30 kg/m^2 for a 187.96 cm (6'2") tall individual.
Route of Administration	Intravenous infusion/injection
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor.

Packaging and Labeling	Study intervention may be provided in 4.7 mL/vial or 6 mL/vial. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-07055480 SB-525 Adeno-associated viral vector with human factor VIII gene

For Japanese sites and Japanese investigators, please refer to Section 10.8.2 for the reporting of study intervention defects.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the IP Manual.

Ordering the IP and Preparation: Details are provided in the IP Manual and it should be reviewed carefully. Once eligibility has been confirmed, the study intervention may be ordered noting that it will take approximately 3 weeks for study intervention delivery. Prior to IP ordering, consider Sections 10.9.1 and 10.9.6.

No participants or third-party payers will be charged for study intervention.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label using central randomization via (IVRS/IWRS)	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS (eg, IMPALA). The site will contact the IVRS/IWRS approximately 3 weeks before the start of study intervention administration for each participant (during baseline period). The infusion site will record the intervention assignment on the applicable case report form, if required.

6.4. Study Intervention Compliance

Study treatment will be infused via infusion pump on Day 1 under supervision by the site staff. The vial lot number, total volume, and infusion time (start and stop times) will be monitored and recorded by the site staff. Full compliance with study treatment infusion is anticipated. Prior to dosing, consider Sections 10.9.1 and 10.9.6. For Japanese sites, please refer to Japan Appendix (Section 10.8.2).

Administration: If a participant does not receive a complete infusion for any reason, she or he will not be rescreened, but will be followed for safety.

6.5. Concomitant Therapy

Any concomitant therapy such as procedures, medication, or vaccine use (including: prescription and non-prescription medications, including over-the-counter and alternative preparations such as herbal remedies, vitamins, and health food supplements) in the 30 days before screening and during screening must be recorded at baseline on the participant's eCRF, according to instructions for eCRF completion. With the exception of FVIII replacement therapy, concomitant therapy throughout the study must be recorded on the eCRF as follows:

- All concomitant therapy (including any COVID-19 vaccinations – see Section 10.9.6) during the short-term monitoring period (up to and including 104 weeks postinfusion).
- The concomitant therapy associated with AEs reported during the long-term monitoring period (Week 105 postinfusion until EOS). See Section 8.3.1 for AE recording requirements.
- All surgical procedures, including elective surgeries, will be recorded throughout the entire study. Additional information regarding surgeries (eg, blood loss and/or transfusion information) will be collected on relevant CRF(s).

The reasons for concomitant therapy will include:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The sponsor's Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants taking medication for a preexisting condition should be on a regimen for at least 3 weeks. Ideally, dosage should not be changed during the first year after PF-07055480 infusion.

Recommended premedications and procedures related to PF-07055480 infusion and to the clinical management of infusion reaction are indicated in the Infusion Reaction Management Guide.

6.5.1. Allowed Therapy

In the event of lack of efficacy, participants may resume their previous treatment plan (ie, treatment before gene therapy administration). Otherwise, FVIII product may be administered when clinically indicated (ie, surgical prophylaxis, traumatic bleed).

During the study, participants will be requested to suspend their FVIII prophylaxis regimen approximately 2 weeks after infusion of PF-07055480, but FVIII replacement therapy is allowed, as needed. The infusion data (specific product, date, time, dosage, reason) is to be recorded in the eDiary.

- For a bleeding event, the investigator/study staff will recommend the appropriate dose of FVIII product to treat the bleed, taking into consideration the most recent and highest PF-07055480-induced FVIII activity levels (by one-stage or chromogenic assays, either from the local or central laboratory) to avoid overdosing. Corrections that increase total FVIII activity levels to >150% may result in an increased risk of potential thrombotic events. World Federation of Hemophilia guidelines for target FVIII levels based on bleed type should be followed.[39]

A participant may resume prophylaxis if the PF-07055480 treatment is not efficacious, defined for this study as:

- FVIII activity after 12 weeks of ≤1% (in the absence of a confirmed FVIII inhibitor) as determined by the central laboratory on 2 consecutive samples collected within a 2-week period and/or over a 4-week period (in the absence of a confirmed FVIII inhibitor);
- 2 or more spontaneous bleeds into a major joint and/or target joint, or
- 3 or more spontaneous bleeds (consisting of joint bleeds and/or significant soft tissue/muscle or other site bleeds). Significant spontaneous bleeds are defined as those that lead to a transient or persistent loss of function.

The investigator is to inform the sponsor's medical monitor before resuming prophylaxis or if prophylaxis has been resumed. Dosing of prophylaxis will be based on the current steady-state FVIII activity level. A participant who resumes prophylaxis may choose to discontinue it; however, before discontinuation, the investigator is to discuss with the Sponsor's medical monitor.

Additional allowed therapies include the following:

- COX-2 inhibitors and topical NSAIDs
- HIV therapy
- Prophylactic anticoagulation therapy in the setting of FVIII activity increases >ULN (please also refer to the “Management Guide for Elevated Factor VIII Activity Levels”)

For guidance about COVID-19 vaccination, refer to Appendix 9 (Section 10.9.6).

Hepatitis B and hepatitis C therapies: For all participants, any use of therapy for hepatitis B and/or hepatitis C, regardless of the time period when taken or association with a reported adverse event, is to be collected and recorded on the CRF (for pre-study therapies, only if known).

HIV therapies: The ongoing therapies taken by the participants with stable HIV at inclusion will be collected as part of the concomitant therapies. If there is a change in HIV therapies during study or if a participant gets infected by HIV while on study, any use of HIV therapy, regardless of the time period when taken or association with a reported adverse event, is to be collected and recorded on the CRF.

6.5.2. Disallowed Therapy

The following concomitant medications are not permitted during the study:

- Blood products such as RBCs, platelets, and fresh frozen plasma, except as required during a surgery or as clinically indicated in the setting of an emergency.
- Medications that may increase the risk of bleeding such as anti-platelet agents (eg, aspirin, clopidogrel); NSAIDs (eg, ibuprofen, naproxen); anticoagulants (eg, warfarin, apixaban), except for the management of FVIII activity increases >ULN (please also refer to Section 6.5.1 and the "Management Guide for Elevated Factor VIII Activity Levels"). Low dose aspirin (<100 mg/day) and PRN use of NSAIDs are allowed where medically necessary. Please contact the sponsor's medical monitor if there are any questions regarding the use of medications that may prolong bleeding.
- Where possible, medications with known hepatoxicity should be avoided. The investigator should inform the sponsor's medical monitor of any plan to administer a medication with known hepatotoxicity.
- Concomitant use of another investigational therapy (for guidance about COVID-19 vaccination, refer to Appendix 9 [Section 10.9.6]); concurrent participation in another interventional clinical study is not allowed.
- Bypassing agents (eg, factor VIIa, activated prothrombin complex concentrate) and nonfactor treatment (eg, emicizumab), except in situations where it is medically necessitated. Antifibrinolytics (aminocaproic acid or tranexamic acid) are also disallowed.

6.6. Dose Modification

No more than a single dose of the study intervention on Day 1 will be administered during this study.

6.7. Intervention After the End of the Study

No further intervention is planned after the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Because no more than 1 single infusion of PF-07055480 on Day 1 will be administered during the study, this section is not applicable. Refer to the IP Manual for information regarding any disruption in administration of the infusion.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. Reasons for discontinuation from the study include the following:

Refused further follow-up;

Lost to follow-up;

Death;

Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such a withdrawal of consent.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported on the CT SAE Report.

7.2.1. Withdrawal of Consent

When a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information, the participant should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed; hence, participants should follow the procedures as described in the study protocol.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The investigational sites for this study may be categorized as follows:

- Study Site: Will screen and follow study participant postinfusion of PF-07055480 for the duration of the study. Some study sites may be approved to carry out infusions within their institution.
- Infusion Center: a site, external from the study site, approved for the administration of PF-07055480.

PF-07055480 is an investigational product, and there is a possible risk of anaphylaxis: Emergency medical equipment will be available at both locations in case the participant has an allergic response, severe hypotensive crisis, or any other reaction to the administration. In the unlikely event that the participant develops sepsis or systemic bacteremia, appropriate cultures and medical management should be initiated.

Screening Period

Screening procedures will be conducted according to the SoA (Section 1.3). The screening period will end and the baseline period will begin when a participant is determined to be eligible for the study.

Baseline Period and Scheduling the PF-07055480 Infusion

Baseline procedures will be conducted according to the SoA. PF-07055480 is to be ordered at the beginning of the baseline period after confirming eligibility. Prior to IP ordering, consider Sections 10.9.1 and 10.9.6. The study intervention will require approximately 3 weeks for shipment. Also, the timing of the participant's next FVIII prophylaxis dose is to be planned to occur on the same day of PF-07055480 infusion (Day 1).

The screening and baseline period may be extended after consulting with the Sponsor's medical monitor. The reason must be recorded in the source documents.

Study sites without necessary infusion facilities will complete Visit 2 at the study site and Visit 3 (Day 1) at the designated infusion center.

Day 1 (at Study Site or at approved Infusion Center)

Day 1 procedures will be conducted according to the SoA. Participants will be hospitalized for 24 hours.

Blood for local and central LFTs has to be collected prior to dosing (up to 3 days prior to Day 1/Visit 3 is acceptable). Mobile phlebotomy can be used as needed. Local LFTs have to

be reviewed before dosing and prior to thawing drug. If the investigator has any clinical concerns regarding the local LFT results, drug should not be thawed. These LFT results may help in the assessment of future LFTs and decisions on when to begin corticosteroid treatment, if necessary.

Note: Participants should be informed that increased alcohol consumption could contribute to abnormally elevated LFT results and thereby delay the infusion of the study drug.

The site staff (or infusion center staff) will confirm that the participant is eligible (see Section 5.1 and Section 5.2) to receive PF-07055480 infusion. Prior to dosing, consider Sections 10.9.1 and 10.9.6. The study intervention should not be thawed and prepared until eligibility criteria are reconfirmed and the participant is physically present at the clinical site (or infusion center).

Participants are expected to bring their current FVIII replacement therapy with them.

If the infusion of PF-07055480 is started for a participant and cannot be completed (receives less than the prescribed dose) for any reason, the protocol does not allow for the participant to be rescreened. The participant will be followed for safety; the data obtained from such participant will not be included in efficacy analyses.

For Japanese sites please refer to Japan appendix (Section 10.8.2).

Study Site Visits (at Study Sites)

Participants should adhere to the visit schedule and procedures in the SoA.

If a participant discontinues or withdraws from the study before Week 260, the early discontinuation visit will follow the same procedures as the Week 260 (EOS) in accordance with the SoA.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test (also see Appendix 9). In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

In the event that any of the safety and/or efficacy related postinfusion procedures listed below cannot be performed according to the timepoints specified in the study protocol, due to 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.

- ECG
- Liver ultrasound
- HJHS
- PROs

8.1. Efficacy Assessments

8.1.1. Hemophilic Bleeding Episodes and Treatment

An eDiary, a handheld device, will be provided to all participants on Visit 1. The participants are required to enter any occurrence of hemophilic bleeding episodes (including date, time, location and etiology) and any exogenous FVIII replacement (including date, time, reason, and dose) required to treat the bleeds in the eDiary.

If bleeding episodes or treatments are not entered during the appropriate time window in the eDiary, participants should communicate all bleeds and all relevant infusion data not entered into the eDiary to the investigator (or appropriate site staff member), and data should be entered by the investigator (or appropriate site staff member) according to the process in place with appropriate source documentation in the participant's medical record. Non-FVIII treatments or procedures to treat bleeds, will be entered by the investigator (or appropriate site staff member) according to the process in place.

The site staff should counsel participants regarding late eDiary entries and emphasize the importance of being compliant with expected eDiary entries (eg, it helps monitor the participant's condition throughout the study) and of reporting all bleeds and all relevant infusion data to the site staff on a contemporaneous basis.

During the site visits, the investigator (or qualified designee) will review the eDiary with participants. Bleeding episodes and any related treatments will be reviewed to ensure consistency between the medical record and/or eDiary (and/or CRF).

In the event that a participant may have 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 (Visit 14). Bleeds and non-prophylactic infusions (eg, on-demand and preventative) should continue to be reported throughout the course of the study. Prescribed FVIII product information will continue to be captured (eg, change in regimen), by the site staff, according to the process in place.

Bleeding episodes requiring treatment with FVIII product (as recommended in the World Federation of Hemophilia guidelines)[39] will count toward the determination of bleeding episode frequency and the eDiary and/or medical record will serve as the source document for bleeding episodes. Definitions of bleeds are in Appendix 7.

8.1.2. Factor VIII activity

8.1.2.1. General Information About Planned Assays

All samples collected from participants for plasma 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 and results will be used to determine steady-state vector-derived circulating FVIII activity levels. As an exploratory objective, both assays performed in central laboratories will be compared.

8.1.2.2. Guidance Related to FVIII Infusions, Bleeds and FVIII Decreases

Measurement of the vector-derived FVIII:C activity levels may be confounded by exogenous factor replacement because participants are allowed to use factor protein products to treat any bleeding events during the study. Thus, calculation of the vector-derived FVIII:C activity levels will take into consideration data entered in the eDiary. As FVIII inhibitors or T-cell mediated immune response may impact the FVIII activity levels, this information will also be taken into account while deriving FVIII:C activity levels.

Refer to guidance related to FVIII activity level measurements and suspected T-Cell activation in Section 8.3.10.

In addition, FVIII activity level should be measured in the below events:

- In the event of an untreated bleed, the measurement should be taken as close to the bleeding event as possible. If the bleed necessitates treatment with exogenous FVIII, the FVIII activity should be assessed post clearance of FVIII product.

- It is recommended to repeat FVIII activity assessment anytime if there is a significant decrease (not attributed to standard fluctuation or to variability of assays) as assessed by the investigator. The medical monitor may be consulted if there are any questions regarding whether a decline in FVIII activity warrants a repeat of FVIII activity level.

8.1.2.3. Guidance Related to Elevated FVIII Activities and Stopping Rule

Participants with FVIII activity levels >ULN should be managed according to the recommendations provided in the “Management Guide for Elevated Factor VIII Activity Levels.”

The guide includes recommendations based on thresholds of FVIII activity levels with 2 main situations described:

(1) participants with elevated FVIII activity levels from 150% to 230% via central or local chromogenic assay or from 230% to 400% via local one-stage assay, and;

(2) participants with elevated FVIII Levels ≥230% via local or central chromogenic assay or ≥400% via local one-stage assay.

According to these levels and after the review of participant's current condition, underlying disease, medical history and risk factors including but not limited to smoking, BMI, prior history of thrombotic event, malignancy, family history, lifestyle, as well as thrombophilia and cardiovascular risk factors, initiation of prophylactic/preventative dose anticoagulation in participants should be considered. Additional laboratory parameters can be recommended (also refer to Section 8.2.7).

FVIII activity may be impacted by corticosteroid treatment. This should be taken into consideration for corticosteroid dosing and weaning.

In the case of an initial thrombotic event suspected to be related to >ULN FVIII activity levels for a participant, the study will be paused and no additional participant will be treated until the circumstances for such an event are assessed and regulatory agencies are notified, if required. In the event of recurrence of a thrombotic event in a participant, the DMC will be convened urgently to assess the event. DMC recommendations will be taken into account in the decision to pause the study.
Should the study be paused, the trial re-start will only be possible after Regulatory Authority approval via substantial amendment, where applicable, based on local/regional regulatory requirements.

8.1.2.4. Recovery Testing

As part of the exploratory assessments of coagulation, recovery of FVIII activity levels may be assessed if prophylaxis is resumed and/or there is a need for prophylaxis to be administered prior to a surgical procedure. The FVIII activity levels measurements can be performed locally or centrally, with repeated samples collected pre-infusion and at 30 minutes post FVIII product infusion.

8.1.3. Joint Assessments

See Appendix 7 for definition of target joints. The investigator will assess the health of the target joint(s), identified at screening, as specified in the SoA. A target joint is considered resolved when there are ≤2 bleeds into the joint within a 12-month period.

8.1.3.1. Hemophilia Joint Health Score (HJHS)

Swelling, on motion Joint assessments will be performed using the HJHS[40] 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. The HJHS is designed for use by physiotherapists. In order to maintain precision and validity of the tool

(score), the developers strongly recommend that the tool be used by physiotherapists/healthcare professionals who have hemophilia-related expertise/experience and have been trained in the use of clinical measures, musculoskeletal assessments and specifically administration of the HJHS. Training on use of the HJHS assessment tools will be provided, by the sponsor, and must be completed by the investigator or designee(s) performing these assessments.

Study participants with prosthetic joints should still have the joints evaluated. The replaced joint should be scored on all items that are possible. Any item that is not tested, for whatever reason, will need to be scored as NE (non-evaluable). This might pertain particularly to the gait skills of running and hopping on 1 leg if the participant is unable to perform the skill or the assessor perceives risk (eg, of bleeding or injury) to the participant if he does perform these skills.

If the HJHS cannot be performed at Visit 10 and/or 13, it is recommended that it be performed at the next subsequent on-site visit or unplanned visit.

8.1.3.2. Ultrasound to Evaluate Joints

A subset of participants (n~20) will undergo ultrasound exams to assess damage within joints by evaluating soft-tissue changes and osteochondral changes. These participants will be chosen based on the expertise of the site, availability of ultrasound at the site, and participant consent to undergo the procedure. The ultrasound scanning protocol will include acquisition of knees, elbows and ankles.

Ultrasound scans will be acquired locally according to the SoA. All details of the ultrasound acquisition including the system will be captured in a separate guide. At a minimum, joint images will be reviewed following the extended ultrasound scale with a final score combining soft-tissue and osteochondral subscores.

If the ultrasound cannot be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4 / Visit 6. If the baseline ultrasound as part of a sub-study could not be performed before or at Week 4 / Visit 6, the study participant does not need to do the post-dosing ultrasounds.

8.1.3.3. X-ray Assessments to Evaluate Joints

Some participants who consent to participate in an optional substudy, except for those participating in Germany, will undergo X-ray assessment 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. 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.[41] Central reading of X-ray images will be performed.

If the X-ray cannot be performed during the screening period, it is acceptable to postpone this testing no later than the Week 4 / Visit 6. If the baseline X-ray could not be performed before or at the Week 4 / Visit 6, the study participant does not need to do the 2 post-dosing assessments.

8.1.4. Other PROs

Patient-reported outcomes implemented in this study are the Haem-A-QoL, the HAL, the HLIQ, and the EQ-5D-5L.[42] Additionally, 6 anchor items have been developed to assess change over time on the Haem-A-QoL, the HAL, and the HLIQ: three global impression of severity items (PGIS) and 3 global impression of change items (PGIC). 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.

The PRO questionnaires should be administered in the following order: Haem-A-QoL, HAL (v2), HLIQ, EQ-5D-5L, PGIS (n=3), and PGIC (n=3).

The PRO questionnaires should be completed in accordance with the SoA during the scheduled site visits using a tablet device that will be provided to each site. Baseline PRO assessments need to be done prior to start of infusion on Day 1 if not done at baseline visit. If the postinfusion PROs cannot be performed at a particular visit, they should be performed at the next subsequent 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 (ie, cannot be taken home) 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.

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

The Haem-A-QoL[43] is a disease specific measure of health-related quality of life in participants 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); Sport 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 Partnerships and Sexuality (3 items). Scores are calculated by domain and a single total score.

8.1.4.2. Hemophilia Activities List (HAL, Version 2)

The Hemophilia Activities List[44,45] (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.

8.1.4.3. 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 (ie, due to hemophilia or due to 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.

8.1.4.4. EQ-5D-5L

Developed by the EuroQoL Group, the EQ-5D-5L (EuroQol, 5 dimensions, 5 levels)[42] 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 (5L) 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.

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

The PGIS-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-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-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.

8.1.5. Imaging Assessments

Please refer to Section 8.1.3.2 and Section 8.1.3.3.

8.1.5.1. Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study but is unrelated to the purpose and beyond the aims of the study.

X-ray images will be reviewed by a central review facility. Central image review is not a complete medical review of the participant. If during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health or reproductive consequence, this finding may be shared with the study sponsor for disclosure to the principal investigator. All follow-up testing and final diagnosis will be left to the discretion of the medical professionals at the site or those with an existing physician-participant relationship. The principal investigator will be responsible for reporting any adverse events identified from incidental findings as described in the Adverse Event Reporting section. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general safety review of all images in accordance with site protocols.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. 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.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body 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/sitting position.

Obtaining oral temperature is preferred, however, if unable to obtain oral temperature, other methods of body temperature assessment such as: tympanic, rectal, axillary, skin, and temporal artery are allowed.

8.2.3. Cardiac Monitoring

- Local single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS and corrected QT intervals (QTc).
- Troponin I will be assessed as described in the SoA.
- A cardiology consultation may be arranged as needed. Refer to SoA for details.

8.2.4. Liver Ultrasound

Local liver surveillance by ultrasound (including HCC detection) is planned as detailed in the SoA. A liver ultrasound scanning guidance will be provided to the sites. Ultrasound images will be acquired locally by an appropriately trained individual. After the first year, all participants will undergo liver ultrasounds yearly, at a minimum, and more frequent ultrasounds may be performed per investigator discretion (eg, participants with risk factors for HCC) or if necessitated to align with participant's standard of care.

This type of hepatic testing will help assess liver structure, and may detect abnormal architecture, tumors, as well as, liver fibrosis. In combination with blood tests, liver testing may help direct the investigative team to early diagnoses of hepatic disease.

8.2.5. Samples for Other Vector Integration Related Testing (if applicable)

In the event that certain findings occur (for example, new abnormalities), further testing may be done as standard of care; for example, repeat testing over time may be ordered. To investigate an abnormal finding, an investigator may recommend a biopsy or tissue collection (liver or other location). In this event, tissue obtained may be requested by the sponsor for further analyses. Tissue analyses may be helpful in establishing (or refuting) a relationship between the adverse event and the gene transfer vector. Analyses would include a vector integration analysis, and possibly quantitation of vector transgene expression, depending on tissue integrity and viability. The consent includes tissue collection; surgical and procedural consents generally cover obtaining samples of tissue for analyses. Likewise, if autopsy material became available for analysis of attribution of vector to an adverse event, tissue would be requested by the sponsor to assess this possibility.

Refer to Section 8.1.5.1 for the management of incidental findings.

8.2.6. Clinical Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section

of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF as an AE, where falling within protocol-specified AE reporting criteria (see Section 8.3.1).

8.2.7. Immunogenicity

All samples collected will be analyzed using a validated analytical method in compliance with standard operating procedures. The samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

8.2.7.1. Analysis of Anti-PF-07055480 Antibodies (ADAs) and Neutralizing Anti PF-07055480 Antibodies

Whole blood specimens of approximately 5 mL to provide a minimum of 2 mL of serum will be collected for determination of total anti-PF-07055480 antibodies (ADAs) and approximately 4 mL of whole blood to provide a minimum of 2 mL of serum will be collected for determination of nAbs to PF-07055480 (anti-AAV6 nAbs and, as part of exploratory endpoints, other nAbs against other AAV serotypes may be assessed) as specified in the SoA (Section 1.3) of the protocol. Instructions for collection and handling of biological samples will be provided by the sponsor.

Those samples may also be used for additional characterization of the immune system and/or evaluation of the bioanalytical methods. Storage will be done in a facility selected by the

sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study.

8.2.7.2. Analysis of FVIII Inhibitor

During all study periods, blood samples will be collected for measurement of inhibitory antibodies against FVIII (inhibitors) as specified in the SoA section of the protocol.

The Bethesda-Nijmegen assay will be used. One BU is defined as the amount of inhibitor that results in 50% residual FVIII:C activity.

Both de novo inhibitors and clinically significant de novo inhibitors will be assessed and are defined based on the following criteria.

- A de novo FVIII inhibitor is defined as a positive central laboratory inhibitor result (inhibitor assay result > 0.6 BU) by the Nijmegen method of the Bethesda assay, in an individual with no prior history of FVIII inhibitors, that is confirmed in a second separately drawn specimen, at least 6 weeks later, that is also assayed at the central laboratory. A local laboratory result indicating possible presence of an inhibitor will prompt an unplanned inhibitor assessment at the central laboratory.
- A de novo inhibitor will be deemed clinically relevant if the occurrence is associated with either complete loss of previously attained FVIII transgene expression (return to baseline FVIII activity level) or the need for the participant to administer non-FVIII coagulation factor products (by-pass agents) in order to achieve efficacy when treating breakthrough bleeding episodes.

In the event of a confirmed inhibitor level for a participant, the study will be paused (no additional participant will be treated) until the circumstances for occurrence of the event are assessed and until notification of regulatory agencies if required. The trial re-start will only be possible after Regulatory Authority approval via substantial amendment, where applicable based on local/regional regulatory requirements.

8.2.7.3. Analysis of Cellular Immune Response by ELISPOT

The ELISPOT assay is a highly sensitive quantitative immunoassay for measuring relevant parameters of T cell activation (the frequency of cytokine-secreting cells at the single-cell level) on PBMC.

Whole blood specimens (approximately 30 mL) will be collected in dedicated tubes to prepare centrally PBMC. Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

T-cell responses to AAV capsid and transgene product will be evaluated as specified in the SoA.

The specimen is to be collected at baseline, and before beginning the corticosteroid treatment when a T-cell response is suspected. If not collected before starting corticosteroid treatment, it must be collected within 24 hours of administering corticosteroids. Analysis should also be repeated approximately 3 weeks after corticosteroid administration and at the end of the

weaning time. Additional specimens may be recommended by the sponsor, in consultation with the investigator, depending on the participant's response to corticosteroid therapy.

As part of understanding of the immunogenicity of the study drug, samples may be used for further characterization and/or evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

8.2.8. Hemostasis Parameters, Thrombotic Potential Assessment and Thrombophilia Parameters

Hemostasis parameters can include aPTT, INR, TAT, TGA, Fibrinogen (activity and antigen) and D-Dimer.
Blood samples to assess aPTT, INR, TAT, TGA and D-Dimer will be collected as defined in the SoA and as specified in the Laboratory Manual.
In addition, all or selected hemostasis parameters listed should also be assessed as clinically needed, and if vector-derived FVIII activity levels >150% of normal are achieved, based on local or central chromogenic assay. Any hemostasis parameter can also be assessed locally. The one-stage assay can lead to higher activity levels, therefore this threshold might be higher and prior measurements / evaluation should be considered. Blood samples for TAT obtained on Day 1 will be used to establish baseline value.

Some parameters related to hereditary or acquired thrombophilia will be assessed for eligibility confirmation, to rule out the presence of AT deficiency, Protein S deficiency, Protein C deficiency, FV Leiden thrombophilia and of the Factor II / Prothrombin gene mutation (G20210A).
Laboratory parameters to be conducted centrally to confirm eligibility include AT activity, Protein C activity, Protein S activity, FV Leiden mutation and the prothrombin G20210A gene mutation. Protein S, protein C and AT antigen levels will be performed as needed.In the setting of FVIII activity levels >ULN and as described in the "Management Guide for Elevated Factor VIII Activity Levels", these assessments (AT, Protein C and Protein S activities and/or antigens) can be repeated centrally and locally as clinically indicated.

8.2.9. Optional Liver Biopsy

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.

Any participant who consents to the procedure will have a liver biopsy via either transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. At least 2 tissue cores will be harvested and additional details for collecting and handling the biopsy specimens are provided in the Laboratory Manual.

FVIII activity levels should be assessed within 7 days before the biopsy and on the day of the biopsy, prior to the procedure. It is recommended that participants have a FVIII activity level of ≥ 50% (or higher, depending on local guidelines and/or investigator discretion) when doing the procedure: as needed, participants may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity levels to an appropriate level, under the supervision/instruction of the investigator, to ensure the safety of the subject during the procedure.

Participants consenting to the optional liver biopsy are recommended to undergo pre-biopsy assessments such as:

At least 28 days before the procedure:

- Physical examination
- Central laboratory safety panels (hematology and clinical chemistry, including LFTs) and hemostasis parameters
- Liver ultrasound (fasting recommended at least 8 hours prior to ultrasound)
- FibroScan or Fibrotest

At least 7 days before the procedure:

- Central and local FVIII activity level assessments
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy before the procedure:

- Participants will be required to observe an 8-hour fasting period before the procedure.
- Brief physical examination
- Central and local laboratory safety panels (hematology and clinical chemistry, including LFTs) and hemostasis parameters
- Central and local FVIII activity level assessments
- As needed, participants may be treated with additional exogenous FVIII replacement products to increase their FVIII activity levels to an appropriate level.

The follow-up care should be done according to the local standard of care. If only a small amount of tissue (< 2 cm) is obtained at the time of the biopsy, the participant may be asked to consent for a second pass. In this case, the original < 2 cm sample should still be retained and handled according to the instructions for handling biopsy specimens in the Laboratory Manual.

Following completion of the biopsy, the subject should remain under observation in the hospital according to the local procedure. Overnight post-procedure observation may be done at the investigator's discretion and/or according to local guidelines.

Whenever applicable, any finding related to the optional biopsy should be further assessed and followed as clinically appropriate to manage the participant's medical care. A hepatologist and/or other specialist clinicians should be consulted if required. Additional liver ultrasound and/or FibroScan may be considered at the discretion of the investigator and/or hepatologist.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or caused the participant to discontinue the study intervention (see Section 7).

Each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

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 (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 (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 5 years after the last administration of the study intervention, or at 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.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE 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, Appendix 3) and AEs will be collected.

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

- SAEs (including medically important events, 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 AEs or SAEs 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.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IECs, and investigators.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- For French sites please refer to France appendix (Section 10.8.1).
- For Japanese sites please refer to Japan appendix (Section 10.8.2).

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

- Details of all pregnancies in female partners of male participants will be collected after the start of study intervention and until end of study participation.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Not applicable for this study.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The DREs for this study include episodes of bleeding related to hemophilia A. The bleeding episode itself is not reported as an AE, unless the bleeding episode meets the criteria outlined below.

Consideration on whether the bleeding event is a DRE is based on investigator determination and bleeding events recorded by the participant in their electronic diary will be reviewed by the investigator and assessed against reporting obligations for AE/SAE.

Bleeding, not due to the participant's hemophilia, will be recorded as an AE, and not a DRE.

In addition, if any of the following conditions apply, then the event must be recorded and reported as an AE or SAE (instead of a DRE):

- Bleeding events that require hospitalization or meet other SAE criteria (see Appendix 3) should be reported as SAEs. When bleeding episodes that meet the SAE criteria are recorded on the AE CRF, the location (site) of the bleed and the etiologic classification as spontaneous or traumatic should be included (as described in Section 8.1.1 and Appendix 2).
- The bleeding event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

- The investigator considers that there is a reasonable possibility that the bleeding event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

Adverse events of special interest include: all medically important events (see Appendix 3) that are to be reported as an SAE, and any clinical thrombotic event or hypersensitivity/infusion-related reactions events assessed as non-serious AEs.

8.3.9. Medical Device Deficiencies

Not applicable

8.3.10. Immunomodulation Optimization (Presumed T-Cell Activation)

A tapering course of oral corticosteroids (eg, prednisone/prednisolone) will be the first consideration for suppression of apparent immune hepatitis. The rationale for this approach is that corticosteroids are effective in severe autoimmune hepatitis, a disease in which hepatocytes are attacked by epitope-specific cytotoxic T-Lymphocyte. The mechanism for this immune reactivity is not clear. It is possible that an elevation in liver transaminases is not due to immune responses.

It is highly recommended that participants be provided with a prednisone prescription before dosing so that it can be filled and ready should treatment be needed.

It is highly recommended that participants who are initiated on corticosteroid treatment be treated with a gastric acid reducer, preferably a proton pump inhibitor (PPI) (eg, omeprazole),

or alternatively a histamine type 2 (H2) antagonist (eg, famotidine) for the duration of the corticosteroid course.

Ultimate decision to initiate corticosteroid therapy is at the discretion of the Investigator.

Due to the importance of timely intervention of corticosteroids, decisions to begin treatment will be based on local laboratory values. Based on gained experience and on guidelines published by the American Association for the Study of Liver Diseases[46], hemophilia B gene therapy study data of the St. Jude Children's Research Hospital and University College London group,[6,47] data from the Phase 1/2a study, treatment with corticosteroids for vector-induced hepatitis should be considered to be instituted as follows:

(1) Transaminase increase:

- Between Day 1 and Day 14 postinfusion, oral corticosteroids should be considered in the following scenarios, in the absence of alternative etiologies:
    - in the presence of ALT above the normal range
    - in the presence of ALT increase ≥ 1.5 fold the lowest baseline value (since screening into the study and prior to infusion) and declining FVIII activity level (not resulting from residual exogenous FVIII).
- From Day 15 to Day 120 postinfusion, oral corticosteroids should be considered in the following scenarios, in the absence of alternative etiologies:
    - in the presence of ALT increase ≥1.5-fold of the lowest baseline value and with FVIII activity level below the normal range or declining.
    - in the presence of ALT above the normal range and if the FVIII activity level is in the normal range (or above).

  Following the trend of ALT values is especially important as it is possible that levels seen postinfusion may be below those seen during screening/baseline. Whenever possible, consider a confirmatory lab draw for ALT , along with FVIII activity, prior to initiating oral corticosteroids. This should not delay the initiation of corticosteroids if clinically indicated.

- Beyond 120 days post-infusion:

  As AAV-specific cellular immune responses are expected to mainly occur within the first months post infusion, if transaminase increase is occurring beyond 120 days postinfusion, the investigator should contact the sponsor's Medical Monitor to discuss prior to initiating corticosteroids unless otherwise clinically indicated.

  Stable FVIII activity levels and/or >ULN levels might not be suggestive of hepatocytes attacked by epitope-specific cytotoxic T-Lymphocytes.

  Corticosteroids should be considered if ALT increase is above normal ranges, AND with FVIII activity level declining.

(2) FVIII activity level decrease:

FVIII activity levels should always be taken into account in the decision to initiate corticosteroid treatment.

- During the first 120 days post-infusion and in the absence of ALT elevations: corticosteroid initiation should be considered if FVIII activity level is below the normal range and is showing consecutive significant decreases (a decline in FVIII activity levels on at least 2 consecutive blood tests independent of transaminase values).

- Beyond 120 days postinfusion, the investigator should contact the sponsor's Medical Monitor to discuss prior to initiating corticosteroids unless otherwise clinically indicated.

Any question about corticosteroid treatment initiation, or any delay or deviation in the initiation of treatment based on the above listed recommendations, should be discussed with the sponsor's medical monitor in the context of the overall clinical management plan of each participant. Ultimate decision to initiate corticosteroid therapy is at the discretion of the Investigator.

The recommended starting dose of oral corticosteroids for the first week is 60 mg or 1 mg/kg (whichever is higher), once daily unless the investigator believes a different regimen should be implemented based on the participant's medical history.

The subsequent prednisolone/prednisone taper should not be started until:

- Transaminases have declined at least 2 consecutive laboratory draws, or have returned to approximately baseline (lowest transaminase value preadministration) levels,

  And

- Any decline in FVIII activity has plateaued.

If FVIII activity decreases or transaminases increase following dose reduction, corticosteroids dose should re-start using the Week 1 dose and taper should not be initiated until the above requirements are met again.

Table 1. Recommended Regimen for Oral Corticosteroids

Schedule (oral corticosteroid treatment regimen)	Prednisolone/Prednisone (mg/day)
Week 1	60 mg or 1 mg/kg (whichever is higher)
Week 2	60 mg or 1 mg/kg (whichever is higher) *
Week 3	40 **
Week 4	30
Week 5	30

Table 1. Recommended Regimen for Oral Corticosteroids

Schedule (oral corticosteroid treatment regimen)	Prednisolone/Prednisone (mg/day)
Week 6	20 ***
Week 7	15
Week 8	10

* Based on the judgment of the investigator, administration of 60 mg or 1 mg/kg once daily oral corticosteroids can be extended to week 3 if the participant has no adverse effect.
** If participant's weight is more than 60 kg, then, decrease week 2 dose in 20 mg/day until 60 mg is reached and continue following above table schedule from week 3 (Example if participant's weight is 90 kg; W1: 90 mg/day , W2: 90 mg/day, W3: 70 mg/day, W4: 60 mg/day, W5: 40 mg/day, W6: 30 mg/day, W7: 30 mg/day, W8: 20 mg/day, W9: 15 mg/day, W10: 10 mg/day).
*** Maintain at 20 mg/day until transaminases return to baseline, then reduce by 5 mg/day until 10 mg/day are achieved then reduce by 2.5 mg/week up to 5 mg daily.
Note: If available, ELISPOT results will be monitored during tapering.

The sponsor's medical monitor can be consulted at any time to discuss either the decision to initiate corticosteroids, escalate immunosuppressive treatment, or taper corticosteroid treatment.

If the tapering criteria are not met after approximately 4 weeks on the increased dose, then the investigator and the sponsor's medical monitor should discuss further management. In some situations, further escalation may be warranted (eg, consideration of more intensive immunomodulatory regimens of combined oral and intravenous corticosteroids or a different immunosuppressant therapy) and in other situations a wean may be initiated (ie, stable but elevated liver function tests without loss of FVIII activity during the treatment period).

Any modification of this approach should be discussed with the sponsor medical monitor.

If corticosteroid therapy is started, measurement of LFTs and of FVIII activity is recommended at least 2 times per week until the end of this therapy.

The following schedule of combined oral corticosteroids and intravenous corticosteroids (methylprednisolone) is recommended if there is no evidence of resolution of transaminase elevation or persistent loss of FVIII activity while on oral corticosteroids treatment alone (Table 2).

Table 2. Recommended Regimen for Combination Intravenous and Oral Corticosteroids

Schedule (corticosteroid treatment regimen)	Oral Prednisolone/Prednisone (mg/day)	Intravenous Methylprednisolone (g/day)
Days 1 to 3	n/a	1
Days 4 to 7	20	n/a
Week 2	60	n/a
Week 3	60	n/a
Week 4	40	n/a
Week 5	30	n/a
Week 6	30	n/a
Week 7	20	n/a
Week 8	10	n/a
Week 9	5	n/a

The investigator will have flexibility in implementing the immunomodulatory regimen because the exact regimen and course will depend on clinical circumstances. If the investigator chooses an immunosuppressive regimen that differs from that suggested above, the investigator should discuss the plan with the Sponsor's medical monitor; this discussion should not delay initiation of immunosuppression.

The long-term side effects of the immunomodulatory drugs to be considered in this study are well characterized. Participants who develop immune hepatitis will be monitored closely to minimize the risk of the side effects. To use the lowest effective dose and to shorten the duration of the immunosuppressive therapies, tapering of the regimen will start as soon as there is evidence of resolution of hepatic transaminases elevation and FVIII activity has plateaued. If available, ELISPOT results will be monitored during tapering. While on immunomodulatory regimens, participants will also be monitored for side effects, such as opportunistic infections. Antibiotics or other medications to minimize the risk of opportunistic infection may be prescribed at the discretion of the investigator. All events related to the use of immunomodulatory drugs (eg, hyperglycemia, weight gain, infections) will be recorded as AEs connected to their use.

- If 2 or more participants are nonresponsive to immunomodulatory regimens, or if the value of the transaminases continues to rise, the Sponsor's medical monitor and investigator will discuss more intensive immunomodulatory regimens. The Sponsor will convey the information to the eDMC.

While on immunomodulatory regimens, participants will also be monitored for adverse events, including infections. Antibiotics or other medications to minimize the risk of opportunistic infection may be prescribed at the discretion of the investigator. All events related to the use of immunomodulatory drugs (eg, hyperglycemia, weight gain, infections) will be recorded as AEs.

For participants with positive HBcAb at screening: HBV surface antigen and HBV DNA will be tested at the end of the tapering course of corticosteroids. If HBV reactivation is noted, management will be based pending a thorough assessment of the participant's clinical status.

8.3.11. Infusion Related Hypersensitivity and Allergic Reaction

In the dose ranging Phase 1/2 study (SB-525-1603), one participant experienced an SAE of severe hypotension and fever, with onset 6 hours after completion of PF-07055480 infusion, treated with PPD . The participant was discharged 24 hours after the end of the PF-07055480 infusion, with no clinical signs remaining.

Hypersensitivity and allergic reactions were previously identified as potential risks of treatment with PF-07055480. An Infusion Reaction Management Guide describes clinical protective measures recommended before, during and after infusion (until hospital discharge). This guide also gives recommendation on the management of such cases.

8.3.12. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant;
- Not performing a flush of the IV line at the conclusion of the study intervention infusion.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if

applicable, any associated AE(s), serious and nonserious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of PF-07055480 greater than 3 x 10^{13} vg/kg of body weight will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with a SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Vector Shedding and Infectivity

Shedding will be assessed by quantitative real time PCR. Samples of plasma, saliva, PBMC, urine, and semen will be collected as specified in the SoA for analysis of vector shedding and infectivity. These samples will be collected as per the instructions provided to the sites to maintain sample integrity for each sample type. Any deviations from that sample handling procedure must be documented and reported to the sponsor.

In the event that a participant is unable to provide any semen for vector shedding over the course of 1 month postinfusion, future attempts to provide semen samples can be stopped provided that 3 consecutive negative PBMC samples are obtained, before no longer being required to follow the restriction within inclusion criteria #6 in Section 5.1.

In the event that samples of plasma, saliva, PBMC, urine, and semen have not yet cleared 20 weeks post infusion, collection can be reduced to every 2 weeks.

Based on preliminary vector shedding data obtained on PBMCs assessed in the ongoing C3731003 study and to limit burden to the participants and collected blood volume, collection of blood to prepare PBMCs and assess shedding post infusion will start from Week 20.

In the event that plasma, saliva, PBMC, urine, and semen have not yet cleared 34 Weeks post infusion, and if home health care service is not available in a country or at a site, collection can be reduced to approximately monthly.

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 DNase treatment for additional characterization.

If further characterization is needed (eg, unusual shedding result), a functional assay may be done to evaluate the infectivity of the virus. This assay will involve in vitro culture of shed material with a permissive cell line.

8.6. Pharmacodynamics

8.6.1. FVIII Antigen

Blood samples will be collected as specified in the SoA and as specified in the Laboratory Manual to measure FVIII antigen levels.

8.6.2. 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 and in the Laboratory Manual.

8.7. Genetics

8.7.1. Specified Genetics

FVIII gene sequencing will be performed where acceptable in accordance with local regulations for the participants who do not have it at baseline (if not previously done and/or not available in the medical file).

A blood sample for DNA isolation will be collected.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

See Appendix 5 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimens for genetics are not included in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

No medical resource utilization and health economics are used in this study.

8.10. Additional Study Assessments

8.10.1. Binding IgG versus IgM

Binding of IgG versus IgM will be measured as specified in the SoA on early timepoints to assess a potential immunoglobulin class switching, which can occur in the first weeks of immune response.

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

8.10.2. Exploratory Cell-Mediated Assays

Cellular responses overtime will be assessed with cell-mediated exploratory assays on PBMCs prepared from whole blood (approximately 48 mL) at timepoints defined in the SoA. Detailed collection, processing, storage, and shipment instructions are provided in the Laboratory Manual.

8.10.3. Archive Plasma Samples

Spare plasma samples (or pre-dose serum on Day 1/Visit 3) for each participant as specified in the SoA. These samples will be archived to repeat testing (if required), for clarification of any clinical or laboratory AE, and for additional exploratory biomarkers (see Section 8.10.4).

8.10.4. Other Exploratory Assays

Remaining serum, plasma and/or PBMC samples may be used to further evaluate the immune responses and study drug mechanism including, but not limited to, the expression of inflammatory markers (eg, IL6 and CRP), markers involved in AAV transduction (eg, EGFR) or any other mechanism-based biomarkers that may be identified in the other ongoing clinical studies with the study drug or other AAV-based gene therapies. Remaining samples may also be used for further development of the study-required laboratory assays.

No samples will be used for genetic analyses. The samples will be destroyed no later than the completion of the clinical study report.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

A gatekeeping process will be applied to control for multiple endpoint comparisons at the primary analysis which is planned after at least 15 months of follow-up postinfusion in at least 50 dosed participants who have completed at least 6 months in the lead-in study (C0371004). The subsequent hypothesis testing will only be performed after success on the previous hypothesis test. The sequence of gatekeeping process and details of statistical methodology will be specified in the SAP.

9.1.1. Estimands

The primary endpoint and the associated hypothesis testing is to demonstrate NI of PF-07055480 to routine prophylaxis on the difference in Total ABR (NI margin of 3

bleeds/year) by comparison of postinfusion of PF-07055480 Total ABR (through at least 15 months up to data cutoff) versus prestudy intervention infusion Total ABR collected during the lead-in study (C0371004) and preinfusion of PF-07055480 in this study (C3731003), in male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII activity ≤1%), who have tested negative for nAb, and have no medical history of FVIII inhibitor.

The corresponding 4 estimand attributes are provided below:

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 nAb, have no medical history of FVIII inhibitor.
Variable	Total ABR (treated and untreated bleedings) from Week 12 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.

Secondary estimands:

The two secondary estimands are:

- the treatment effect of PF-07055480 with respect to FVIII activity levels >5% at 15 months postinfusion or resumption of FVIII prophylaxis regimen (if necessary).

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 nAb, have no medical history of FVIII inhibitor.
Variable	FVIII activity level >5% at 15 months (65 weeks) post IP infusion.
Intercurrent Event	• Any sample taken within 72 hours for standard half-life products and 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.

Estimand Attribute	Description
	• Any FVIII activity levels after the resumption of FVIII prophylaxis regimen (if necessary) will be imputed with 0.9%. Participants who resume prophylaxis regimen prior to Month 15 post PF-07055480 infusion will be considered as having FVIII activity level ≤5%. • Participants who discontinue from the study 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 to a null hypothesis of percentage ≤68% using an exact binomial test at one-sided alpha = 0.025.

- the ABR:

Estimand Attribute	Description
Population	Male participants ≥18 years of age with moderately severe to severe hemophilia A (FVIII activity ≤1%), who have tested negative for nAb, have no medical history of FVIII inhibitor.
Variable	ABR (treated bleedings) from Week 12 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	ABR post PF-07055480 infusion will be compared to participants' ABR on prior FVIII prophylaxis regimen using a repeated measure negative binomial regression model. Model-based estimated difference in mean ABR and the 95% CI will be reported. In addition, percent reduction in mean ABR and the corresponding 95% CI will be estimated.

9.2. Sample Size Determination

Approximately 70 participants from the lead-in Study C0371004 will be enrolled and eligible participants will be assigned to study intervention to achieve a desired sample size of at least 50 dosed participants completing at least 15 months of follow-up postinfusion. All participants are expected to be dosed in this single armed study. The number of participants may exceed 50, because all C0371004 participants who meet the eligibility criteria will be allowed to participate in this study.

Sample size for the primary analysis based on treated ABR assumptions: A sample size of at least 50 dosed participants who have completed at least 15 months post PF-07055480 infusion will provide at least 95% power (one-sided test with alpha=0.025) to demonstrate noninferiority of gene therapy compared to prophylaxis treatment on the difference in ABR with an NI margin of 3.0 bleeds/year. The sample size and power determination were performed using simulations (5000 samples) with a negative binomial distribution of ABR for FVIII prophylaxis regimen. This sample size is based on an assumed 4.0 bleeds/year in the ABR of prophylaxis regimen and 1.0 bleed/year in the ABR through 15 months post

PF-07055480 infusion. The correlation between PF-07055480 and FVIII prophylaxis treatment was assumed to be 0.2 in simulations based on prior internal data with BeneFIX (Study B1821002).[48]

The choice of the NI margin is based on the FDA guideline[49] of selecting a margin based on historical data and EMA guideline[50] and ICH guidelines[51,52,53], on the choice of NI margin, taking into consideration the constancy assumption, and using the "95%-95%" method.

The NI margin is based on the effect of prophylaxis treatment over on-demand treatment (as the reference treatment and the active control), which is expressed by a mean difference in ABR in a single arm trial with a switch from on-demand to prophylaxis using a paired comparison (see Appendix 7 for definitions of factor replacement regimens). Historical data were investigated among prior Pfizer hemophilia studies. This enabled selection of individual participant level data that would closely match the inclusion/exclusion criteria. Studies having both prophylaxis and on-demand treatment were selected to provide a within-study treatment difference estimate. The following 3 studies satisfied these criteria: B1821010 (BeneFIX),[54] B1821002 (BeneFIX),[48] and B1831004 (Xyntha/ReFacto).[55] Both Hemophilia A and Hemophilia B data were considered due to similarity in the benefit of prophylaxis versus on-demand treatment seen in ABR with respective factor replacement therapies. The mean ABR difference between prophylaxis and on-demand treatment was estimated using an additive negative binomial model. Based on the lower bound of the confidence interval of this estimate, the on-demand ABR is assumed to be higher by at least 16.8, which will be considered as M1 in the noninferiority test setting.

Given the large effect size of prophylaxis treatment (over on-demand therapy), an appropriate value for M2 was selected in order to preserve a sufficiently large proportion of this effect. Preservation levels of 75, 80, and 85% of M1 correspond to noninferiority margin values of 4.2, 3.4, and 2.5 bleeding events/year, on an absolute scale, respectively. A value of 3.0 for M2 (approximately 82% of the M1 effect preserved) is both clinically meaningful and yielding a reasonable sample size for establishing efficacy.

Clinical justification of the noninferiority margin is further supported from a review of observed ABR from real world studies and clinical studies. The Sponsor has compared prophylaxis efficacy results for the FVIII product moroctocog alfa (AF-CC) in the real-world setting (Study 3082B2-4432)[56] and in the clinical trial setting (Study 3082B2-310)[57]. Study 3082B2-4432 was a postauthorization study in which 154 participants with FVIII:C <1% received an investigator-prescribed regimen of prophylaxis treatment. Study 3082B2-310 was a preauthorization clinical trial in which 94 participants with FVIII:C ≤2% (including 87 participants with FVIII:C ≤1%) received a protocol-specified prophylaxis treatment regimen. The ABR was 8.43 during the during prophylaxis treatment in Study 3082B-4432, whereas in Study 3082B2-310 the mean ABR observed during prophylaxis was 3.9. In the recently published lead-in study of emicizumab in noninhibitor hemophilia A participants (≥12 years of age) the on-demand ABR was 36.1 and the FVIII prophylaxis regimen ABR was 5.0 for treated bleeds[58]. The results of prophylaxis treatment from the Pfizer clinical studies are within the range of results observed in other studies and therefore indicate that they are representative of hemophilia A prophylaxis results. Given the

range of mean ABR observed in various clinical trials and real-world data (0 - 8.9), a value of 3.0 represents a reasonably conservative margin of NI.

Adjustments Based on Total ABR as The Primary Endpoint

In the absence of internal historical data for total bleeds, the results of emicizumab publications of HAVEN1 and HAVEN3 studies were used as a reference.[59,60] A treatment difference (in terms of mean number of bleeds) between the on-demand treatment (no prophylaxis) versus the prophylaxis (emicizumab) treatment and the ratio of treatment difference in total bleeds over that in treated bleeds were calculated from the two referenced studies. It is then assumed that the treatment difference ratio of the on-demand treatment (no prophylaxis) compared to the prophylaxis (emicizumab) treatment will be similar to the ratio in comparison of the prophylaxis treatment to the gene therapy. Table 3 shows that the difference in mean Total ABR is 12% to 23% higher than the difference in mean treated ABR, resulting in a geometric mean increase of 17% for Total ABR versus treated ABR.

Table 3. Estimated Effect of Treated Bleeds and All Bleeds Per Year in Emicizumab Studies

	HAVEN1 (Inhibitors)			HAVEN3 (No inhibitors)		
	Prophylaxis	On demand	Treatment difference	Prophylaxis	On demand	Treatment difference*
Treated ABR	2.9	23.3	20.4	1.5	38.2	36.7
Total ABR	5.5	28.3	22.8	2.5	47.6	45.1
Ratio (Total/Treated)	1.90		1.12	1.67		1.23

*Difference between the on-demand treatment and the emicizumab prophylaxis in the once weekly group.

Adjustment of M1 and M2 :

M1 of 16.8 (difference in mean treated ABR between FVIII product prophylaxis and on-demand treatment based on internal studies listed above) is expected to be equivalent to 19.66 (ie, 16.8*1.17) when considering mean Total ABR. Preservation levels of 75%, 80%, and 85% of M1 will correspond to noninferiority margin values of 4.9, 3.9, and 2.9 bleeding events/year, on an absolute scale, respectively. A value of 3.0 for M2 (approximately 84.7% of the M1 effect preserved) is both clinically meaningful and yielding a reasonable sample size for establishing efficacy based on Total ABR.

Adjustment of assumptions:

According to Table 3, the ratio of Total ABR over treated ABR in the emicizumab prophylaxis treatment group was 1.90 in the HAVEN1 study and 1.67 in the HAVEN3 study. It is assumed that the relationship between Total ABR and treated ABR with gene therapy is similar to that with emicizumab prophylaxis therapy.

Study C3731003 assumes the treated ABR under the standard FVIII prophylaxis regimen is 4 bleeds/year based on related data in 3 internal studies and 1 bleed/year (a 75% reduction from 4 bleeds/year) with the gene therapy. Based on the ratio of 1.90 for Total ABR over treated ABR from HAVEN1 (ie, the higher ratio of Total/Treated observed), it is assumed the Total ABR will be 2 bleeds/year after the gene therapy (ie, 1*1.90 approximately equal to 2). In addition, the lowest mean treated ABR reported among the 3 internal FVIII product studies was 2.6; as a conservative approach, Total ABR will be assumed to correspond to 5 bleeds/year (ie, 2.6*1.90 approximately equal to 5) for prior prophylaxis treatment. This assumption is equivalent to a 60% reduction in mean Total ABR after gene therapy compared to prophylaxis treatment.

Based on the simulations described above, the sample size for the primary analysis based on Total ABR remains unchanged. A sample size of at least 50 dosed participants who have completed at least 15 months of follow-up post PF-07055480 infusion will provide at least 95% power (1-sided test with alpha=0.025) to demonstrate noninferiority of gene therapy compared to prophylaxis treatment based on a difference in mean Total ABR with an NI margin of 3.0 bleeds/year.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF and meet all inclusion/exclusion criteria.
Dosed/Safety	All participants enrolled in the study and who receive the study intervention.
Evaluable	All participants enrolled in the study and who receive the study intervention and have no significant interruption of efficacy measurement and no major protocol deviation.
Efficacy	All participants in the “Dosed” population who have completed at least 6 months 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.

9.4. Statistical Analyses

The primary analysis will be conducted when at least 50 dosed participants with 6 months of follow up in the Lead_In study (C0371004) have reached at least 15 months of follow-up postinfusion (ie, data cutoff for primary analysis).

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. The overall probability of Type 1 error for primary statistical tests, and other tests included in the multiple testing procedure, is controlled at .05 (or one-sided .025). For the primary analysis, the Type I error will be

controlled using a hierarchical testing approach whereby the primary hypothesis of NI of Total ABR from Week 12 through at least 15 months (up to data cutoff) post PF-07055480 infusion compared to the Total ABR pre-PF-07055480 infusion will be tested first followed by a comparison of the percentage of participants with FVIII activity level >5% at 15 months to a null hypothesis of percentage ≤68% using an exact binomial test at one-sided alpha = 0.025, and then a NI test on the ABR from Week 12 through at least 15 months (up to data cutoff) postinfusion compared to the ABR pre-PF-07055480 infusion. Subsequently a test for superiority of AIR, annualized FVIII consumption, Total ABR, and ABR will be performed. Additional secondary endpoints including PROs may also be tested following the test for superiority of ABR using the same gatekeeping approach. More information about gatekeeping approach is included in the SAP.

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 1/2 study (C3731001).

Any minor changes to the statistical methodology stated in the protocol will be described in the SAP. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

The primary analysis is planned after at least 15 months of follow-up postinfusion in at least 50 dosed participants, with endpoints in the table below. The planned endpoints after the primary analysis, so called final analysis, are focused on extended efficacy and longer-term safety.

Category of Endpoint	Primary Analysis Statistical Analysis Methods
Primary	• Total ABR (treated and untreated bleedings) from Week 12 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). A repeated measure negative binomial regression model will be used to test NI with NI margin = 3 bleeds/year at one-sided alpha level = 0.025. If the noninferiority on Total ABR is established, subsequently testing for superiority will 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 1/2 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% is determined so it could be rejected when the observed percentage is greater than 80%. • ABR from Week 12 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) and analyzed separately using the same method applied to Total ABR.

Category of Endpoint	Primary Analysis Statistical Analysis Methods
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) or summarized. • FVIII Activity from Week 12 through 15 months postinfusion of PF-07055480 will be summarized with descriptive statistics. • FVIII activity level will be summarized by visit with descriptive statistics. In addition, the percentage of participants with 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 through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be compared to preinfusion (under SOC FVIII prophylaxis replacement regimen) and analyzed using a paired t-test. • Annualized FVIII consumption, from Week 12 through at least 15 months (up to data cutoff) postinfusion of PF-07055480, will be analyzed using the same method applied to AIR. • ABR of specific type (spontaneous and traumatic) from Week 12 through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be analyzed separately using the same method applied to Total ABR. • ABR by location (in joints, in target joints, or in soft tissue) from Week 12 through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be analyzed using the same method as Total ABR. • Total ABR (treated and untreated) by location from Week 12 through at least 15 months (up to data cutoff) postinfusion of PF-07055480 will be analyzed using the same method as Total ABR. • The percentage of participants (from Week 12 through at least 15 months (up to data cutoff) postinfustion of PF-07055480) without bleeds 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 PF-07055480 will be summarized and compared to baseline to assess the improvement from baseline if baseline is available.
Exploratory	Will be described in SAP finalized before database lock.
Category of Endpoint	**Final analysis** **Statistical Analysis Methods**
Secondary (all final analysis endpoints are considered secondary in this study)	Analyses will be performed at the following intervals (Month 15, Years 2 through 5). Details will be described in the SAP finalized before database lock.
Exploratory	Comparison of FVIII activity assays and other exploratory analyses will be described in the SAP finalized before database lock.

Category of Endpoint	Primary Analysis Statistical Analysis Methods
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 EOSV).
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.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	No primary safety endpoint.
Secondary	Descriptive analyses of SAE, AE of special interests, lab abnormality, etc. will be conducted.
Exploratory	Will be described in the SAP finalized before database lock.

9.4.3. Other Analyses

Pharmacodynamics (as FVIII antigen levels), and other exploratory analyses will be described in the SAP finalized before database lock.

9.5. Interim Analyses

No interim analysis is planned. 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 assessment.

9.5.1. Data Monitoring Committee (DMC)

This study will use an 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 SUSAR). The eDMC charter describes the role of the eDMC in more detail.

The recommendations made by the eDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions,

which may include summaries of aggregate analyses of study endpoints and of safety data, to regulatory authorities and investigators, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable ICH GCP Guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require Regulatory Authority approval before implementation, where applicable based on local/regional regulatory requirements, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

<u>Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP</u>

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational

product, Pfizer should be informed immediately. For Japanese sites please refer to Japan Appendix, Section 10.8.2.4.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant [or their legally authorized representative] should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/EC or study center.
- The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and

correct his or her personal data and to withdraw consent for the processing of his or her personal data.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the IRB/EC-approved ICF(s) during their participation in the study as required per local regulations
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- For German sites please refer to Country-Specific Appendix (Section 10.8.3.3).
- For Japanese sites please refer to Country-Specific Appendix (Section 10.8.2.4).

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.
- Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.
- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred.

All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- The sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

Refer to Section 9.5.1 for information on the DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted.

These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for all Pfizer-sponsored interventional studies that are in scope of EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing authorization packages/submissions

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data Sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the

investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Study Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained. For Swedish sites, please refer to Country-Specific Appendix (Section 10.8.4).
- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Data Monitoring Plan.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the Contract Research Organization if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the

applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the ISF.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 3 will be performed by the CL unless otherwise indicated in Table 4.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4. Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit RBC Indices: MCV, MCHC, MCH ABO: only if unknown at screening		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	Blood urea nitrogen Serum creatinine Potassium Sodium Chloride Bicarbonate Glucose Phosphate		
Lipid panel (8 h of fasting)	LDL VLDL	HDL Triglycerides	Total cholesterol
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones		
Cardiac monitoring	Troponin I		
Liver function tests (CL and LL)	Albumin Total bilirubin Direct bilirubin Indirect bilirubin	ALP AST ALT	Total protein GGT LDH
FVIII activity (CL and LL)	Central laboratory: Chromogenic and one stage clotting assays Local laboratory: routine assay		
Coagulation	Global hemostasis markers • Main group: aPTT (in ratio), INR, TAT, TGA, D-dimer • As needed: Fibrinogen (activity and antigen) Thrombophilia related parameters • AT, Protein C, Protein S activities and antigens (free and total)		

Table 4. Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters	
	• Genetic analyses: FV Leiden thrombophilia mutation and FII / Prothrombin gene mutation (G20210A)	
FVIII inhibitor	FVIII inhibitor testing (Nijmegen Bethesda), (LL only if clinically indicated)	
AAV neutralizing antibody	Anti-AAV6 neutralizing antibodies nAbs against other AAV serotypes (for cross reactivity)	
ADA	Anti-PF-07055480 antibodies	
Immunology	PBMC preparation for ELISPOT assays (specific to AAV6 and to the transgene) and for other exploratory cell-mediated assays Binding IgG versus IgM antibody response	
Exploratory pharmacodynamics markers	Von Willebrand Factor FVIII Antigen levels	
Vector shedding and infectivity	Vector shedding will be detected in plasma, urine, saliva, semen, and in PBMC Infectivity will be performed if applicable	
Hepatitis B and hepatitis C	Hepatitis B surface antigen (HBsAg) Hepatitis B core total antibodies (HBcAb) HBV DNA	Hepatitis C virus AB HCV RNA Quantitative
Liver fibrosis	• FibroTest/FibroSURE (including α2-macroglobulin, apolipoprotein A1 and haptoglobin)	
Biomarker for hepatic carcinoma	α-Fetoprotein	
HIV	HIV-1/HIV-2 antibody screen HIV-1 RNA (qualitative) and CD4+ count if positive antibodies	
Spare plasma	Plasma (or pre-dose serum on Day 1/Visit 3) will be stored for repeat and/or the testing of additional exploratory biomarkers of the immune response and study intervention mechanism of action	
FVIII genetic testing	Mutation in FVIII gene If not available in the source documents only	

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: Is associated with accompanying symptoms. Requires additional diagnostic testing or medical/surgical intervention. Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from

lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

- In this study, the following events that occur poststudy treatment infusion are considered medically important events and should be reported as SAEs:

  1. Any participant develops clinical thrombotic event (with the exception of IV infusion-site thrombophlebitis).

  2. Any participant develops a confirmed FVIII inhibitor.

  3. Any participant develops clinically significant hypersensitivity reaction (eg, bronchospasm and anaphylaxis). Infusion related reactions should be reported as serious only if they meet serious criteria.

4. Any participant develops a hepatic malignancy.
5. Any participant develops drug-related elevated hepatic transaminases that fail to improve or resolve through treatment with immunosuppressive regimens.
6. Any occurrence of a malignancy assessed as having reasonable possibility relatedness to study drug.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

During the Short Term Monitoring Period (up to and including 104 weeks postinfusion)

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE (including the medically important events – as defined in Section 10.3.2)	All	All
Non-serious AE	All	None
Exposure to the study intervention under study during pregnancy and occupational exposure	All AEs/SAEs associated with exposure during pregnancy. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy. Include all AEs/SAEs associated with occupational exposure.

During the Long Term Monitoring Period (Week 105 until EOS Visit)

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE (including the medically important events – as defined in Section 10.3.2)	All	All
Non-serious AE determined to be related to the study intervention by the investigator; and/or where causality is unknown.	All	None
Exposure to the study intervention under study during pregnancy and occupational exposure	All AEs/SAEs associated with exposure during pregnancy. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.** • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements. • If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor" and "In addition, if the investigator

determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Pfizer Safety by telephone.
- Contacts for SAE reporting can be found in the ISF.

SAE Reporting to Pfizer Safety via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the ISF.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

Contraception guidance for the male participants until at least 3 consecutive ejaculate samples test negative for vector shedding as follows:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below.
    - Agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person.

Collection of Pregnancy Information:

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.

- The results of genetic analyses may be reported in the clinical study report or in a separate study summary, or may be used for internal decision-making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

    - Samples for specified genetic analysis (see Section 8.7) will be stored for up to 5 years or other period as per local requirements or will not be stored beyond the completion of this study (eg, clinical study report finalization).

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;
- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.The participant should return to the investigator site and be evaluated as soon as possible, preferably within

48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's Law, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and ALP. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Unique to PF-07055480 is the potential for T-cell induced hepatocyte destruction. In some cases, presentation of AAV capsid protein by MHC to the surface of a hepatocyte can trigger CD8 cell mediated targeting of hepatocytes. This presents asymptomatically with a rise in LFTs and/or a decline in FVIII activity levels. This effect is not due to direct hepatocyte toxicity rather it is an immunologic response. This immunologic reaction has been shown in prior studies and more particularly in 2 participants in the Phase 1/2a dose escalation study who have both responded to a short course of corticosteroids.

10.7. Appendix 7: Factor Replacement Regimens and Bleed Definitions

Definition of Factor Replacement Regimens

Prophylaxis Therapy: The regularly scheduled and regimented administration of factor replacement therapy to prevent bleeding.

Preventative Therapy: Infusion of clotting factor that is given in anticipation of a planned physical activity that has a high risk of injury (eg, surgery or sporting activity).

On-Demand Therapy: The administration of factor replacement therapy only at the time of an acute bleeding event.

Definition of a Bleed

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 bleed occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated or a bleed occurring at a different site from the original bleed regardless of the time from last injection.

Definition of a Bleed Location

Target Joint: Defined as a major joint (eg, 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.

Joint Bleed: A bleeding episode characterized by rapid loss of range of motion as compared with baseline that is associated with any combination of the following: pain or an unusual sensation in the joint, palpable swelling, and warmth of the skin over the joint.

Muscle Bleed: An episode of bleeding into a muscle, determined clinically and/or by imaging studies, generally associated with pain and/or swelling and functional impairment.

Definition of Bleed Types

Spontaneous Bleeds: Bleeding for no apparent/known reason particularly into the joints, muscles, and soft tissues.

Traumatic Bleeds: Bleeding event occurring for an apparent/known reason.

Note: Bleeds related to a procedure/surgery such as hematomas/bruising resulting from any surgeries or invasive procedures (eg, tooth extractions, venipuncture, or subcutaneous drug administrations) or invasive diagnostic procedures (eg, lumbar puncture, endoscopy with biopsy) would NOT be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. France Appendix

This appendix applies to study sites located in France.

Per France regulations, a France-specific protocol appendix is to be included in the final approved protocol to capture some operational items not included in the mandatory contract format for France (ie, French "Contract Unique"), which Pfizer includes in standard contract language for other countries. The following items included do not impact the conduct of the trial, the safety or integrity of the participant, or use of their data:

1. GCP Training

Prior to enrollment of any participants, the investigator and any sub-investigators will complete the Pfizer-provided GCP training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

No participants or third-party payers will be charged for study intervention.

3. Record Retention

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

4. SUSARs

Pursuant to a sponsor's safety reporting obligations under 21 CFR 312.32(c)(1), Pfizer will report to the investigator all Serious Unexpected Suspected Adverse Reactions ("SUSARs"). Investigator will receive and review SUSAR reports and report SUSARs to the responsible IRB/IEC according to institution's guidelines. Institution will retain SUSAR reports consistent with the above paragraph (Record Retention) and Appendix 1.

10.8.2. Japan Appendix

This appendix is only for investigators at Japanese sites.

10.8.2.1. Study Intervention Defects Definitions

Defect: Refers to lack of function of the study intervention (see Section 6.1), causing generally poor conditions where the cells cause adverse reactions that affect the human body, irrespective of what stage of manufacture, delivery, storage or use the defect occurs.

10.8.2.2. Reporting Criteria

All study intervention defects are to be reported to the sponsor within 24 hours of investigator awareness (see Section 10.8.2.3) if any of the points listed below apply. Note: The reporting of study intervention defects will not result in any change to the reporting of AEs as described in Section 10.3 (Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

- Occurrence of study intervention defects directly or indirectly leads to SAEs (see Section 10.3.2) of a participant/user/other person.
    - OR
- Study intervention defects have not actually led to SAEs but may possibly lead to SAEs of a participant/user/other person.

For product complaints that do not meet the reporting criteria above, refer to the Investigational Product Complaints section of the study Investigational Product (IP) Manual for detailed reporting procedures.

10.8.2.3. Reporting Procedures

The following procedures are to be followed in order to report the Study Intervention Defect(s) to the sponsor:

1. Study intervention defects information should be recorded, as completely as possible, on the *Investigational Drug Product (Regenerative medicine products) Complaint Submission Form* located in the Investigator Site File (ISF).

2. The form should be submitted electronically to sponsor within 24 hours of being aware of an intervention defect.

3. After the complaint is received by the sponsor, a close out memo will be generated. This close out memo will be provided to the study site.

10.8.2.4. Japan-Specific Protocol Wording

10.8.2.4.1. Section 6.4 Study Intervention Compliance

The study drug will NOT be administered to multiple Japanese participants on the same day of the administration to the first Japanese participant.

10.8.2.4.2. Section 8.3.4 Regulatory Reporting Requirements for SAEs

The sponsor will report SAEs that impact study status to the Japan sites approximately 24 hours of Pfizer Japan receipt of the report.

10.8.2.4.3. Section 10.1.1 Regulatory and Ethical Considerations

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately. This information should be shared with Japan sites approximately 24 hours after Pfizer Japan is aware of this information.

10.8.2.4.4. Section 10.1.3 Informed Consent Process

When a minor participant (defined as less than 20 years old) is included in this study in Japan, written informed consents will be obtained from both the participant and his legally acceptable representative.

10.8.3. Germany Appendix

This appendix is only for investigators at German sites.

10.8.3.1. Section 5.1 Inclusion Criteria

7. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. German adult participants need to be of age AND be able to consent themselves in writing to be eligible to participate in the study.

10.8.3.2. Section 5.2 Exclusion Criteria

17. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study. In Germany, employees of the sponsor, CRO, or study site are not eligible to participate in the study even if they are not involved directly with the conduct of the study.

18. Unable to comply with scheduled visits, treatment plan, laboratory tests and other study procedures for up to 6 years post study drug infusion in the investigator's judgement. In Germany, participants committed to an institution by virtue of an order issues either by the judicial or the administration authorities are not eligible to participate in the study.

10.8.3.3. Section 10.1.3 Informed Consent Process

German adult participants need to be of age AND be able to consent themselves in writing to be eligible to participate in the study.

10.8.3.4. Section 1.3 Schedule of Activities (SoA)

Participants seen at German sites will not be permitted to undergo X-ray testing for this study.

10.8.3.5. Section 8.1.3.3 X-ray Assessments to Evaluate Joints

Participants seen at German sites will not be permitted to undergo X-ray testing for this study.

10.8.4. Sweden Appendix

This appendix is only for investigators at Swedish sites.

10.8.4.1. Section 10.1.7. Data Quality Assurance

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 30 years after study completion. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.

10.9. Appendix 9: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.9.1. Participants Who Test Positive for COVID-19

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed.

If a participant tests positive for COVID-19, the study site staff should continue to follow their routine practice guidelines for COVID-19, for example: the participant may receive study intervention when he has **no COVID-19 symptoms for 10 days** and:

- tests negative for COVID-19
- Or
- continues to test positive for COVID-19, but at least 21 days since the first positive COVID-19 test.

Prior to dosing:

- sites should continue to follow their routine practice guidelines for COVID-19 (for example, ruling out an underlying pneumonia by performing O_2 saturation [via pulse oximetry device] and/or a chest x-ray, check D-dimer, or other relevant assessment, if applicable).
- And
- consult with the sponsor.

10.9.2. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow-up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method. Confirm that the participant is adhering to the contraception method(s) required in the protocol.
- Review bleeding episodes and FVIII infusions reported in the eDiary.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.9.3. Home Health Visits

The home health care service (3rd party provider contracted to Pfizer or its designee) will be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. Biological samples may be collected during a home health visit in order to perform: standard safety tests (hematology and clinical chemistry including liver function tests), hemostasis/coagulation parameters, lipid panel, troponin I, α-fetoprotein, FVIII activity, FVIII antigen, FVIII inhibitors, total and neutralizing anti-AAV antibodies, Elispots, exploratory cell mediated assays, IgG/IgM class switching assay, von Willebrand factor, vector shedding, spare plasma. Additionally, vital signs and PROs may be collected during a home health visit by the same health care service.

10.9.4. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse event (SAE) and appropriate medical intervention provided.

It is recommended that the investigator discuss temporary or permanent discontinuation of concomitant medications with immunosuppressive activity with the study medical monitor.

10.9.5. Guidance for Missed Visits/Assessments and Protocol Deviations

Every effort should be made to ensure that protocol required tests and procedures are completed as described. However, it is anticipated that from time to time, there may be

circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the participant. When a protocol required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study must be considered. For participant discontinuation reporting in the CRF: select the most appropriate status for discontinuation; if the discontinuation is associated with the current COVID-19 pandemic, enter "COVID-19" in the "Specify Status" field.

In the event that any of the safety and/or efficacy related postinfusion procedures listed below cannot be performed according to the timepoints specified in the study protocol, due to 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.

- ECG
- Liver ultrasound
- HJHS
- PROs

10.9.6. Guidance for COVID-19 Vaccination

Vaccination against COVID-19 is not contraindicated as a part of this study. However, key considerations for trial participants receiving COVID-19 vaccinations are:

a. Potential for a reduced response to vaccine if administered while participant is receiving corticosteroids

b. Potential infusion related reactions to gene therapy or vaccine occurring simultaneously.

As such, the following recommendations are provided:

1. For participants receiving COVID-19 vaccination prior to administration of the study drug, it is recommended that the infusion of the study drug should not occur until at least 4 weeks after last injection with the vaccination (some vaccines may require more than 1 injection). For participants who have already received the study drug, the COVID-19 vaccine may be administered once the participant has reached at least 12 weeks of follow-up post-study drug infusion if the participant is not currently on corticosteroids. If the participant is on corticosteroids at 12 weeks postinfusion, it is

recommended vaccination is delayed until the participant has been weaned off of corticosteroids.

2. It is recommended to follow WFH guidelines on how to administer the vaccine (see https://www.hemophilia.org/News/COVID-19 Vaccination Guidance from NHF, WFH, EAHAD, and EHC for the Bleeding Disorders Community). Specifically:

    a. Intramuscular injection

    b. Ensure exogenous factor is available in the event of a bleeding event

    c. Consider an infusion of exogenous factor prior to vaccine administration if in the investigator's opinion the last factor activity level places participant at risk of developing a bleeding event associated with the administration of the vaccine.

3. Please contact the Pfizer medical monitor if you have any questions concerning COVID-19 vaccination in study participants.

4. COVID-19 vaccinations should be reported to the study investigator and reported as a concomitant medication on the CRF.

Ultimate decision-making regarding administration of the COVID-19 vaccine will be between the investigator and the study participant.

10.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 9 (03 February 2023)

Overall Rationale for the Amendment: change related to dose calculation, implemented in response to FDA, and addition of an optional liver biopsy substudy.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.3 Schedule of Activities **Section 2.3.1. Risk Assessment** **Section 3. Objectives, Estimands, and Endpoints** **Section 8.2.8. Optional Liver Biopsy**	Addition of an optional liver biopsy substudy (and recommended related assessments).	The objective of this exploratory substudy is to assess the vector integration in the liver, to examine the liver tissue for any alteration and to provide a better understanding of the mechanism of action of the study drug in the liver.	Substantial
Section 6.1 Study Intervention(s) Administered	Participants will now have their dose ($3x10^{13}$ vg/kg) calculated based on the use of the IMP nominal concentration of $1.0x10^{13}$ vg/mL.	This change is being made to facilitate dosing calculation at the sites and is not secondary to a safety concern.	Substantial
Section 2.3.1 Risk Assessment	Update to the list of important risks (including terminology).	Changes made for consistency with latest IB update to align with recent EMA feedback on the list of important risks for other AAV-based gene therapy programs in hemophilia. No change per se to the risk profile of giroctocogene fitelparvovec.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 1.1 Synopsis **Section 2.1 Study Rationale** **4.1 Overall Design** **9.2 Sample Size Determination**	Update to the sample size from 63 eligible participants to 70 eligible participants.	Changes made to account for potential attrition (following the study temporary pause).	Substantial
Section 8.3.10 **Immunomodulation Optimization (Presumed T-Cell Activation)**	As implemented via the PACL dated 12 September 2022: **c**onsolidation and further refinement of the guidance for initiation of corticosteroid treatment to more clearly incorporate considerations about ALT levels, FVIII activity levels along with time from giroctocogene fitelparvovec infusion.	The revisions are for clarity and completeness, to further assist investigators in their decision making. All considerations included in protocol Section 8.3.10 continue to be for guidance only as the decision on whether and when to initiate corticosteroid treatment in a study participant remains with the investigator, based on clinical judgement.	Nonsubstantial
Section 1.3 Schedule of Activities **Section 8.5.1 Vector shedding and infectivity**	As implemented via the PACL dated 12 December 2022: Blood collection to prepare PBMCs and assess shedding in this matrix will start from Week 20.	Update made based on preliminary data from the already dosed participants and the observed prolonged clearance time in PBMCs, to limit burden to the participants and collected blood volume. This change will have no impact on the assessment of clearance time in PBMCs. Available data for the already dosed participants will allow assessment of early shedding kinetics and peak related data.	Nonsubstantial
Section 9.3 Populations for Analyses	Minor clarifications/corrections	Updates made for consistency with SAP	Nonsubstantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 9.4.1 Efficacy Analyses			
Section 9.5.1 Data Monitoring Committee (DMC) **Section 10.1.1 Regulatory and Ethical Considerations** **Section 10.1.4 Data Protection** **Section 10.1.6 Dissemination of Clinical Study Data** **Section 10.1.7 Data Quality Assurance** **Section 10.1.9 Study and Site Start and Closure** **Section 10.1.10 Publication Policy**	Clarifications	Updates made for consistency with the sponsor's protocol template regularly updated to ensure regulatory compliance.	Nonsubstantial

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).
Editorial, grammatical, formatting, and administrative changes were made throughout the document.

Amendment 8 (21 November 2022)

Overall Rationale for the Amendment: change related to dose calculation, implemented in response to FDA.

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
Section 6.1 Study **Intervention(s) Administered**	Country specific change for Brazil, Canada, Saudi Arabia, Taiwan and Turkey: participants will now have their dose ($3x10^{13}$ vg/kg) calculated based on the use of the	This change is being made to facilitate dosing calculation at the sites and is not secondary to a safety concern.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or Nonsubstantial
	nominal concentration of $1.0x10^{13}$ vg/mL.		
Section 8.3.10 **Immunomodulation Optimization (Presumed T-Cell Activation)**	As implemented via the PACL dated 12 September 2022: **c**onsolidation and further refinement of the guidance for initiation of corticosteroid treatment to more clearly incorporate considerations about ALT levels, FVIII activity levels along with time from giroctocogene fitelparvovec infusion.	The revisions are for clarity and completeness, to further assist investigators in their decision making. All considerations included in protocol Section 8.3.10 continue to be for guidance only as the decision on whether and when to initiate corticosteroid treatment in a study participant remains with the investigator, based on clinical judgement.	Nonsubstantial

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 7	26 May 2022	**1. Safety Updates Following Occurrence of a Thrombotic Event:** - 'conditions associated with increased thromboembolic risk such as inherited or acquired thrombophilia' is added within the exclusion criterion # 4 listing the history of chronic diseases and of conditions excluding participants (Section 5.2. Exclusion Criteria). - Measurement of laboratory parameters to assess the presence of inherited or acquired thrombophilia (protein S deficiency, protein C deficiency, antithrombin deficiency, FV Leiden thrombophilia and G20210A prothrombin (FII) mutation) will be performed centrally. These assessments are added in the Schedule of Activities (Year 1 and Years 2 to 5 [Section 1.3]), in Section 8.2.7 (Hemostasis Parameters, Thrombotic Potential Assessment and Thrombophilia Parameters) and in Appendix 2. These laboratory parameters were previously recommended to be conducted locally in the event of elevated FVIII levels as described in the protocol **S**ection 8.2.7 and in the "Management Guide for Elevated Factor VIII Activity Levels". - Addition of Fibrinogen (activity and antigen) as part of the global hemostasis parameters in Section 8.2.7 (Hemostasis Parameters, Thrombotic Potential Assessment and Thrombophilia Parameters) and in Appendix 2. - The risk section is updated to include a deep vein thrombotic (DVT) event reported in a C3731003 participant with prior history of PPD (Section 2.3.1. Risk Assessment). Additional mitigations described above are also added. - The protocol stopping rule related to the occurrence of thrombotic events was amended; in case of an initial thrombotic event in a

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		participant, the study will be paused as initially defined, whereas the DMC will be urgently convened in case of the recurrence of a thrombotic event in a participant before making a decision about study continuation or pause. (Section 2.3.1 [Risk Assessment], Section 4.1 [Overall Design] and Section 8.1.2.3 [Guidance Related to Elevated FVIII Activities and Stopping Rule]). **2. Revisions in Response to US FDA Comments on Study Endpoints:** - 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. - The assessment of all endpoints related to bleeds and infusions (including Total ABR, ABR and AIR) will start from 12 weeks post study drug infusion (instead of 4 weeks), corresponding to the estimated FVIII activity level steady state onset. Synopsis (Section 1.1), Schema (Section 1.2), Study Rationale (Section 2.1), Objectives, Estimands, and Endpoints (Section 3), Overall Design (Section 4.1), Scientific Rationale for Study Design (Section 4.2), Section 9.1.1 (Estimands), Section 9.2 (Sample Size Determination), Section 9.3 (Populations for Analyses), Section 9.4 (Statistical Analyses), and Section 9.4.1 (Efficacy Analyses). - The justifications for the population size and NI margin are updated based on the use of Total ABR instead of ABR as the primary endpoint. Section 9.3 (Populations for Analyses) and references. - The percentage of participants with FVIII activity levels ≥40% at each visit will be provided within FVIII activity analyses (Section 9.4.1 (Efficacy Analyses)). Section 9.4.1 (Efficacy Analyses). **3. Clarification of the Recommendations for Immunomodulation Optimization:** Section 8.3.10 (Immunomodulation Optimization) is updated to clarify guidance to start corticosteroid treatments based on gained experience from the management of the already dosed participants in the Phase 3 study, including the confirmation of the absence of any other etiologies before starting treatment and guidance about late initiation of corticosteroids **4. Clarification on eDiary Completion Requirements:** Section 8.1.1 (Hemophilic Bleeding Episodes and Treatment) is updated to clarify (1) guidance for participants non-compliant with eDiary requirements and (2) bleed and infusion entry requirements after prophylaxis resumption (and from Week 78), to limit the burden to participants.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		5. Clarification on the Planned Long Term Follow-Up Study (After the End of this Phase 3 Study): Synopsis and Section 4.1 (Overall Design). **6. Clarification on the Exclusion Criterion #5:** Clarification about the history of malignancies in participants; except for adequately treated basal or squamous cell carcinoma of the skin or a surgically removed benign neoplasm not requiring chemotherapy and/or radiotherapy, participants with any history of a neoplasm (including hepatic malignancy) that required treatment (eg. chemotherapy, radiotherapy, immunotherapy), are excluded. Any other neoplasm that has been cured by resection should be discussed between the investigator and the sponsor. Section 5.2 (Exclusion Criteria). **7. Minor clarification on the duration of Lead-In Study:** Synopsis and Section 4.1 (Overall Design). **8. Added clarification on the gatekeeping process:** Section 9.1 (Estimands and Statistical Hypotheses). **9. Inclusion of Protocol Administrative Change Letter (PACL) and Country-Specific Amendment:** Added clarification to Section 8.5.1 (Vector Shedding and Infectivity) and in the Schedule of Activities (Year 1 and Years 2 to 5 [Section 1.3]) to allow for decreased frequency of sample collection for shedding assessment after 34 weeks in the study in the event that samples have not yet cleared at this time and if home-health care is not available at a site or country. **Editorial, grammatical, formatting, and administrative changes were made throughout the document.**
Amendment 6	13 January 2022	**1. Revisions in Response to US FDA Comments:** – Primary analysis moved from 12 months postinfusion to 15 months postinfusion, corresponding to 12 months of follow-up after Week 12. – Change of the key secondary FVIII activity endpoint initially based on the geometric mean FVIII activity level (from onset of steady state to 12 months postinfusion) to the proportion of participants having more than 5% FVIII activity level at 15 months postinfusion. The geometric mean FVIII activity level (from onset of steady state to 15 months postinfusion) has been retained as a secondary endpoint. – Total ABR added as another key secondary endpoint. The study will therefore include 2 key secondary endpoints. – Removal of the interim analysis initially planned at 12 months postinfusion on 20 participants.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Synopsis (Section 1.1), Schema (Section 1.2), Study Rationale (Section 2.1), Objectives, Estimands, and Endpoints (Section 3), Overall Design (Section 4.1), Scientific Rationale for Study Design (Section 4.2), Section 9.1.1 (Estimands), Section 9.2 (Sample Size Determination), Section 9.3 (Populations for Analyses), Section 9.4 (Statistical Analyses), and Section 9.4.1 (Efficacy Analyses). **2. Safety Updates:** – To support a consistent approach to manage participants with FVIII activity >ULN postinfusion, a guide including recommendations for Investigators has been developed and endorsed by the eDMC ("Management Guide for Elevated Factor VIII Activity Levels"). Key recommendations included in this guide are summarized in Factor VIII activity (Section 8.1.2) and Hemostasis Parameters and Thrombotic Potential Assessment (Section 8.2.7). The guide is referenced in Schedule of Activities (Section 1.3), Risk Assessment (Section 2.3.1), Allowed Therapy (Section 6.5.1), and Disallowed Therapy (Section 6.5.2). – Addition of a stopping rule in case of a thrombotic event suspected to be related to >ULN FVIII activity levels (Overall Design [Section 4.1] and Factor VIII activity [Section 8.1.2]). – The risk of "Overexpression of transgene and activity of transgene in treated patients/thrombotic events" in the risks/mitigations table has been updated to refer to the cases of participants with >ULN FVIII activity levels, to the implemented recommendations to manage these participants, and to the added stopping rule (Risk Assessment [Section 2.3.1]). – Minor update of exclusion criterion #4 to further clarify that participants with a history of thrombotic events should be excluded and that this is not open to investigator discretion (Exclusion Criteria [Section 5.2]). **3. Inclusion of Protocol Administrative Change Letter (PACL) and Country-Specific Amendment:** – Inclusion of PACL#3 changes: – Clarified the preparation of the spare sample collected before dosing (on Day 1 or 3 days before Day 1); serum samples, instead of plasma should now be stored on that day (Schedule of Activities, Year 1 [Section 1.3], Archive Plasma Samples [Section 8.10.3], and Table 3 Protocol-Required Laboratory Assessments [Section 10.2]). – Provided additional recommendations for liver ultrasounds (Schedule of Activities, Years 2 to 5 [Section 1.3] and Liver Ultrasound [Section 8.2.4]).

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		– Provided additional recommendations while the participant is treated with corticosteroids, including the duration that a participant may be on an increased corticosteroid dose and clarification addressing opportunistic infections (Immunomodulation Optimization [Presumed T-Cell Activation] [Section 8.3.10]). – Provided clarifications of the procedures to be repeated for screen-failed participants being rescreened (Screen Failures [Section 5.4]). – Provided clarifications for the collection of therapies for HIV, hepatitis B and hepatitis C to be recorded on the CRF (Allowed Therapy [Section 6.5.1]). – Provided clarifications for the assessment of Troponin I (Schedule of Activities, Year 1 and Years 2 to 5 [Section 1.3]). – Provided clarification about the schedule of ELISPOT testing after the initiation of corticosteroid treatment (Schedule of Activities, Year 1 and Years 2 to 5 [Section 1.3]). – Inclusion of changes made upon German Regulatory Authority request and initially implemented in Germany only via Amendment 5. **4. Minor clarifications and administrative changes** – Clarification on the schedule of spare plasma (Schedule of Activities, Year 1 and Years 2 to 5 [Section 1.3]). – Re-addition of an asterisk which had been deleted by mistake in the Schedule of Activities, Day 1, FVIII activity (CL, LL), LFT (CL, LL) and FVIII antigen (CL) (Section 1.3, Year 1). Added clarification to specify that FVIII activity assessment on Day 1 is optional. – Added clarification for Phase 1/2 data to specify that no "confirmed" inhibitor has been observed (Summary of Clinical Experience with PF-07055480 [Section 2.2.1] and Risk Assessment [Section 2.3.1]) for consistency with Phase 3 definitions. – Added clarification to specify FVIII inhibitor must be confirmed to be reported as a medically important event as already specified in Section 8.2.6.2, and deleted information about laboratory test as a confirmed inhibitor refers to the protocol definition including both laboratory and clinical aspects (Section 10.3.2). – Added clarification to Section 8.5.1 (Vector Shedding and Infectivity) and in the Schedule of Activities (Year 1 and Years 2 to 5 [Section 1.3]) to allow for decreased frequency of sample collection for shedding assessment after 20 weeks

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		in the study in the event that samples have not yet cleared at this time. – Added clarification to Section 8.10.4 (Other Exploratory Assays) to specify that remaining study samples may also be used for needed additional validations of study-required laboratory assays. **5. Editorial, grammatical, formatting, and administrative changes were made throughout the document.**
Amendment 5	13 May 2021	**Changes implemented in response to German Regulatory Authority (PEI)'s comments, applicable to Germany only:** **Synopsis - Overall Design (Section 1.1) and Overall Design (Section 4.1):** - Added text about the planned long-term follow-up after the 5-year period in this study to clarify that all participants will be invited to enter a separate multi-country, non-interventional, registry-based study to allow for at least 10 years of follow-up post-gene therapy infusion.
Amendment 4	09 April 2021	**1. Revisions in response to US FDA Comments:** • Description of changes: - Revised Interim Analysis to occur at 12 months postinfusion instead of 6 months post steady state with the same endpoints as for the Primary Analysis (ABR as primary, FVIII activity level as key secondary, AIR as secondary). o Changes in Synopsis (Section 1.1), Schema (Section 1.2), Study Rationale (Section 2.1), Objectives, Estimands, and Endpoints (Section 3), Overall Design (Section 4.1), Scientific Rationale for Study Design (Section 4.2), Section 9.1.1 (Estimands), Section 9.2 (Sample Size Determination), Section 9.4 (Statistical Analyses), Section 9.4.1 (Efficacy Analyses) and Section 9.5 (Interim Analyses). - Added Hypothesis testing for the Interim Analysis. o Changes in Section 9.1.1 (Estimands), Section 9.4 (Statistical Analyses), Section 9.4.1 (Efficacy Analyses) and Section 9.5 (Interim Analyses). - Added text to specify that the onset of FVIII activity steady state is expected to be reached at the beginning of Week 9 postinfusion (based on Phase 1/2 Study C3731001 data). o Changes in Synopsis (Section 1.1), Study Rationale (Section 2.1), Objectives, Estimands, and Endpoints (Section 3), Overall Design (Section 4.1), Scientific Rationale for Study Design (Section 4.2), Section 9.1.1 (Estimands),

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 9.4 (Statistical Analyses), and Section 9.4.1 (Efficacy Analyses). - Updates to the study sample size justification at the Primary Analysis with addition of more information on the simulations made and correlation assumed to define the study sample size. o Changes in Section 9.2 (Sample Size Determination). - Deleted justifications of the sample size of the population at the Interim Analysis as hypothesis testing is now included. The study sample size is based on the Primary Analysis. The sample size n=20 for the Interim Analysis is based on treatment effect observed using historical data and is sufficient to demonstrate statistical significance. o Changes in Section 9.2 (Sample Size Determination).
		2. Alignment with recent updates in C0371004 Lead-In study: Clarification of the duration of follow-up on routine FVIII prophylaxis therapy in C0371004 required prior to enrollment into C3731003 to align with changes made to the duration of follow-up in the C0371004 protocol. In the C0371004 protocol, the exact duration of follow-up for each individual participant may be: (1) 6 months or longer as dictated by enrollment into the subsequent dosing study (eg. for site activation delay, participant availability); (2) shorter than 6 months after at least 50 participants are followed for at least 12 months in this study (C3731003). - Changes in Synopsis (Section 1.1), Study Rationale (Section 2.1), Overall Design (Section 4.1), Scientific Rationale of the Study (Section 4.2), Inclusion Criteria #2 (Section 5.1) and in Figure 1.
		3. Addition of secondary endpoints to assess FVIII activity level by visit, in addition to the geometric mean from steady state to W52**:** – Added in Synopsis (Section 1.1) and in Objectives, Estimands and Endpoints (Section 3).
		4. Readjustment to the frequency of the FVIII antigen, FVIII activity levels and LFTs assessments with additional timepoints added closer to Week 52 (IA and PA) whilst some assessments at earlier timepoints were removed to avoid additional burden on participants**:** (1) decrease of the frequency from weekly to monthly (from W20) for FVIII antigen, (2) decrease from twice a week to weekly from W13 to W20 for FVIII activity, (3) decrease from weekly to every 2 weeks from W22 to W34 for FVIII activity and LFTs (4) addition of 2 laboratory visits to allow an approximate monthly assessment of FVIII activity and LFTs in the second half of year 1, (5) added general guidance about FVIII activity measurements in case of a significant decrease or in case of bleed: – Changes in Schedule of Activities (Section 1.3).

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		5. Addition of an exploratory endpoint to further assess coagulation and more specifically FVIII recovery post administration of FVIII product during the study (post gene therapy). This may be done at the time of a planned surgery or if a participant resumed prophylaxis. – Added in Objectives, Estimands and Endpoints (Section 3) and in Factor VIII Activity (Section 8.1.2).
		6. Clarification of inclusion criterion #2 (Section 5.1): to allow participants to have their eligibility confirmed earlier, participants can start the Study C3731003 screening visit (V1) while still in the non-IMP Lead-In Study C0371004.
		7. Minor statistical clarifications: • **Clarification of the population for the primary analysis:** "50 evaluable" replaced by "50 dosed completing 12 months," to avoid confusion with the evaluable population as defined in the table in Section 9.3 as "all participants enrolled in the study and who receive the study intervention and have no significant interruption of efficacy measurement". – Changes in Synopsis (Section 1.1), Study Rationale (Section 2.1), Overall Design (Section 4.1) and Sample Size Determination (Section 9.2). • **Clarification for consistency across the document:** for the planned efficacy analyses comparing PF-07055480 to prior FVIII prophylaxis, all preinfusion data will be considered as prior routine FVIII prophylaxis, including both the C0371004 Study and the PF-07055480 preinfusion period of this study (C3731003). • **Clarification of the period to assess ABR, AIR and associated endpoints:** the analyses will exclude the first 3 weeks of prophylaxis (approximately 2 weeks is recommended to participants), and therefore will start from Week 4 (Day 22). There is no change to analyses initially planned. • **Addition of the efficacy population definition** for consistency with SAP in Populations for Analyses (Section 9.3)**.**
		8. Added guidance to the sites or clarifications: • **For clarity, addition of an introductory sentence to present the Phase 3 program,** including the C0371004 Lead-In study and the C3731003 Phase 3 study (Section 1.1 and Section 2). • **Updates to the Phase 1/2 C3731001 study data:** – Changes in Synopsis (Section 1.1), Study Rationale (Section 2.1), Summary of Clinical Experience (Section 2.2.1) and Justification for Dose (Section 4.3) • **Minor clarification for HIV testing** in case of serological evidence of HIV, both CD4+ count and viral load should be

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		assessed to confirm acceptable CD4+ count and undetectable viral load: – Changes in Schedule of Activities (Section 1.3), Exclusion Criteria #16 and Table 3 (Appendix 2 – Clinical Laboratory Tests) • **Deletion of the collection of tuberculosis vaccination history in Schedule of Activities (Section 1.3):** this will be reviewed and discussed by the investigator if corticosteroid treatment is started, as part of all other practical recommendations for the monitoring, prevention and management of systemic corticosteroid-induced adverse events. • **Revision of exclusion criterion #15:** added clarification about liver fibrosis assessment to specify that in case of inconsistent results between modalities, Pfizer should be contacted (Section 5.2). • **Added recommendations for immunomodulation treatments:** in Immunomodulation Optimization (Presumed T-Cell Activation) (Section 8.3.10), it is now specified that (1) participants should be provided with a prednisone prescription before dosing and (2) addition of guidance if the selected immunosuppressive regimen differs from what is proposed in the protocol. • **Added guidance for liver ultrasound, more specifically in case of abnormal findings** (Section 8.2.4). • **Added guidance in case FVIII activity levels are superior to 150%** including local/central parameters to be tested and assay considerations in Hemostasis Parameters and Thrombotic Potential Assessment (Section 8.2.7). • **Added guidance for the selection of the appropriate dose of FVIII product in case of a bleeding event** occurring during the study (post gene therapy infusion) (Section 6.5.1). This guidance is based on the most recent and highest available FVIII activity in an effort to avoid achieving levels that are supratherapeutic (>150%). • **Added clarifications on hypersensitivity and infusion-related reactions** in Adverse Events of Special Interest and in Definition of SAE (Sections 8.3.8 and 10.3.2).
		9. Inclusion of Protocol Administrative Change Letters (PACLs) and country-specific amendments: • **Inclusion of PACL#1 changes:** – Implementation of COVID-19 measures added into Appendix 9. Related changes for added flexibility of some assessments (ECG, liver ultrasound, joint X-rays, joint ultrasound, HJHS, PROs), when not impacting the scientific integrity and the quality of the data have been added to the Schedule of

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Activities (Section 1.3). Sections 8, 8.1.3.2, 8.1.3.3 and 8.1.4 have also been updated accordingly. – Joint X-Rays are now optional for participants as specified in the Schedule of Activities (Section 1.3) and in Section 8.1.3.3. – Update of joint ultrasounds timepoints in the Schedule of Activities (Section 1.3): addition of an earlier assessment (6-month postinfusion) to focus on early changes, with the deletion of the 5-year ultrasound and the total number of assessments remaining 3. – Added recommendation for participants who are initiated on corticosteroid treatment, to be treated with a gastric acid reducer for the duration of the corticosteroid course to prevent any gastrointestinal event (Schedule of Activities (Section 1.3) and Section 8.3.10). – Clarifications about adverse events of special interest and added definition (Sections 8.3.8 and 10.3.2). – Clarification of the definition for intercurrent event related to the FVIII activity level variable (Sections 3 and 9.1.1). A conservative approach was selected and all samples taken within 96 hours of exogenous FVIII replacement therapy with no distinction between standard and extended half-life will be excluded from the assessment of steady state FVIII post vector infusion. – Minor correction: deletion of MPV parameter from the list of Hematology/RBC Indices parameters (Section 10.2). This parameter cannot be assessed centrally due to low stability of this parameter and is not compatible with shipment time. This deletion has no impact on the safety monitoring of participants and will be assessed locally whenever needed. • **Inclusion of PACL#2 changes:** – Guidance for participants who test positive for COVID-19 (Section 10.9.1) and for COVID-19 Vaccination (Section 10.9.6) added within the COVID-19 Appendix. – Reference to COVID-19 Appendix added as applicable in Schedule of Activities, 6.2 (Preparation/Handling/Storage/Accountability), 6.4 (Study Intervention Compliance), 6.5 (Concomitant Therapy), 6.5.1 (Allowed Therapy), 6.5.2 (Disallowed Therapy) and Section 8 (Study Assessments). – Addition of more guidance for missed ECGs, HJHS, PROs and liver ultrasounds if assessments missed for COVID-19, in Section 8 (Study Assessments and Procedures) and in Section 10.9.5 (Guidance for Missed Visits/Assessments and Protocol Deviations).

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		• **Inclusion of changes made upon Sweden Regulatory Authority request and initially implemented in Sweden only via Amendment 3 listed below.** • **Inclusion of Japan-specific PACL changes (v10Dec20):** – Clarification of the informed consent process in terms of the age criteria and definition of minor participants in Sections 10.1.3 and 10.8.2.4. • **Inclusion of changes made upon UK Regulatory Authority request and initially implemented in the UK only via Amendment 2 listed below.**
		10. Editorial, grammatical, formatting, and administrative changes were made throughout the document.
Amendment 3	12 March 2021	**Changes upon Sweden Regulatory Authority request, applicable to Sweden:** **Benefit/Risk Assessment (Section 2.3):** – Added a more detailed benefit/risk assessment so that the investigator can easily form his/her own opinion of the benefit/risks for a particular participant to be included in the current clinical trial. **Data Quality Assurance (Section 10.1.7) and Sweden Appendix (10.8.4):** – Amended Data Quality Assurance section and created new appendix to specify, according to current Swedish regulations, essential documents in an ATMP trial must be retained for at least 30 years. **Regulatory and Ethical Considerations (Section 10.1.1):** – Amended to address the procedure for amendments to the protocol.
Amendment 2	09 December 2020	**Changes upon UK Regulatory Authority (MHRA)'s request, applicable to the UK:** **Exclusion Criteria (Section 5.2):** – At Regulatory Authority's request, clarification of the exclusion criterion #5 to specify malignancies and more specifically hepatic malignancies, as part of the concurrent clinically significant major diseases or conditions for exclusion. **Participant Discontinuation/Withdrawal from the Study (Section 7.2):** At Regulatory Authority's request, deletion of a sentence about protocol deviations management. **Analysis of FVIII Inhibitor (Section 8.2.6.2):** – At Regulatory Authority's request, added clarification to confirm that in case of study pause following confirmed inhibitory antibodies against FVIII for a participant, the trial

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		re-start will only be possible after Regulatory Authority approval via substantial amendment. **Regulatory and Ethical Considerations (Section 10.1.1):** At Regulatory Authority's request, added clarification to specify that any substantial amendment to the protocol will require Regulatory Authority approval before implementation.
Amendment 1	13 May 2020	**As per FDA request, update of the endpoint to support the early approval pathway:** for the first interim analysis planned in 20 participants, FVIII activity level will be monitored during 6 months after FVIII activity level steady state is reached, instead of 6 months post study drug infusion. Additional visits for laboratory assessments (using home health/mobile phlebotomy services as applicable) have been added as described in the schedule of activities to allow comprehensive FVIII monitoring (activity and expression). Liver function tests will also be performed. Related updates were made in: - Synopsis, including Figure 1 (Section 1.1 and Section 1.2) - Schedule of Activities (Section 1.3) - Study Rationale (Section 2.1) - Objectives, Estimands, and Endpoints (Section 3) - Study Design (Section 4) - Statistical Considerations (Section 9.2, Section 9.4.1 and Section 9.5)
		Objectives, Estimands, and Endpoints (Section 3): • Revision of text to clarify the primary endpoints for interim and primary analyses. As per FDA request, the primary endpoint to support the early approval pathway has been updated: for the first interim analysis planned in 20 participants, FVIII activity level will be monitored during 6 months after FVIII activity level steady state is reached, instead of 6 months post study drug infusion. In addition, wording for other endpoints and estimands have been revised for clarity (Section 3). • For clarity and consistency with the statistical analyses planned, the secondary endpoint of the interim analysis has been deleted from Section 3, and is now only displayed within Section 9.5 (Interim Analyses). • Immunogenicity: reference to the ELISPOT method deleted from the endpoint. • Deletion of wording within the list of endpoints related to the joint health objective as analyses are detailed in SAP.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		Minor Clarifications in Inclusion/Exclusion Criteria (Section 5.1 and Section 5.2): • Inclusion Criteria #4 and 5 were revised for clarity. • Inclusion Criterion #7 was revised to meet German Ethics Committee requirements in Section 5.1. • Exclusion Criteria #6, 7, 8, and 13 were revised for clarity. • Exclusion Criterion #8 was revised to clarify specifics of repeat testing and that "hepatic" encephalopathy is exclusionary, in relationship with unstable liver disease. • Exclusion Criterion #15 was revised to clarify specifics of liver fibrosis testing. • Exclusion Criteria #17 and #18 were revised to meet German Ethics Committee requirements in Section 5.2. **Lifestyle Considerations Clarification (Section 5.3):** • It was added that participants should be informed that alcohol consumption could contribute to abnormally elevated liver function test (LFT) results and delay infusion of the investigational product (IP) infusion, and increased alcohol consumption was defined. **Screen Failures (Section 5.4):** • Text was updated and revised for consistency with updates in Exclusion Criterion #8. **Study Intervention(s) Administered (Section 6.1):** • Updated for clarity and consistency, and wording was added to refer to new country-specific language in Section 10.8. **Preparation/Handling/Storage/Accountability (Section 6.2):** • Text added to confirm the absence of charge for participants and payers related to study intervention. **Study Intervention Compliance (Section 6.4):** • Wording was added to refer to new country-specific language in Section 10.8. **Concomitant Therapy (Section 6.5)**: • Clarified that all surgical procedures, including elective surgeries, will be recorded throughout the entire study. Added note in SoA.

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Minor clarifications in disallowed therapies. **Study Assessments and Procedures (Section 8), Schedule of Activities (Section 1.3):** • Vital signs were revised from **oral** temperature to **body** temperature to permit flexibility with methods utilized by the sites (Section 1.3 and Section 8.2.2). • Vital signs were revised from **upright** position to **upright/sitting** position for clarity (Section 1.3 and Section 8.2.2). • When applicable, fasting is recommended for Fibroscan (Section 1.3). • Local LFTs results have to be reviewed prior to study drug infusion. An up to 3 days time window is therefore allowed to collect blood for local and central LFTs (Section 1.3 and Section 8). • A reasonable margin of error and guidelines have been added in SoA for FVIII product infusion on Day 1 (prior to study drug) (Section 1.3). • eDiary: clarification of data collection process (Section 8.1.1). • HJHS: clarification added for participants with prosthetic joints (Section 8.1.3). • Section 8.2.7.1 and Section 8.2.7.3: blood volumes updated or clarified. **Statistical Considerations (Section 9):** • The reference to the ITT population has been deleted (Section 9.3) as it is not applicable for the study. • As specified for Section 3, the secondary endpoint of the interim analysis has been deleted from Section 3, and is now only displayed within Section 9.5 (Interim Analyses). Wording in Section 9.5 has been revised for clarity. • Estimands and endpoints wording revised for clarity. Whenever applicable, the “within-participant” wording has been deleted to avoid confusion, as the comparison of lead-in and Phase 3 data will be made using analysis models and not using participant-level difference. **Adverse Events and Serious Adverse Events:** • Section 8.3.10: Wording was revised regarding immunomodulation optimization (for participants who develop hepatitis transaminitis) to more clearly describe elevations in liver transaminases and to eliminate any

DOCUMENT HISTORY		
Document	**Version Date**	**Summary and Rationale for Changes**
		potential delays in initiating corticosteroid treatment. Specific examples were added. **Efficacy - FVIII:** • For clarity and flexibility, it was added that as FVIII inhibitors or T-cell mediated immune response may impact the FVIII activity levels, this information will also be taken into account while deriving FVIII:C activity levels. **Appendices:** • Clinical Laboratory Tests table was revised for consistency and minor corrections were made (Section 10.2). • A country-specific requirements appendix was added for France as per France RA and ethical requirements (Section 10.8.1). • A country-specific requirements appendix was added for Japan as per Japanese RA requirement (see Section 10.8.2). Corresponding cross references were added to appropriate sections. • A country-specific requirements appendix was added for Germany as per German regulations and RA requirements (see Section 10.8.3). Corresponding cross references were added to appropriate sections. **Editorial, grammatical, formatting, and administrative changes were made throughout the document, including changes to the List of Abbreviations and changes to comply with protocol template format (eg, added wording for clarification within study population, participant discontinuation, and safety sections).**
Original protocol	10 December 2019	N/A

10.11. Appendix 11: Abbreviations

Abbreviation	Definition
α-fetoprotein	alpha-fetoprotein
AAV	adeno-associated virus
AAV2/6	adeno-associated virus vector 2/6
ABR	annualized bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AF-CC	albumin-free cell culture
AFP	alpha-fetoprotein
AIR	annualized (FVIII) infusion rate
ALP	alkaline phosphatase
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AT	antithrombin
ATMP	Advanced Therapy Medicinal Products
BDD	B-domain deleted
BMI	body mass index
BU	Bethesda Units
CD4+	cluster of differentiation 4
CD8+	cluster of differentiation 8
CFR	Code of Federal Regulations
CI	confidence interval
CL	central laboratory
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
COX-2	cyclooxygenase-2
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRU	clinical research unit
CSR	clinical study report
CT SAE	clinical trial serious adverse event
DILI	drug-induced liver injury
DMC	data monitoring committee
D**NA**	deoxyribonucleic acid
DNase	deoxyribonuclease
DRE	disease related event
DVT	deep vein thrombosis
EAHAD	European Association for Haemophilia and Allied Disorders

Abbreviation	Definition
ECG	electrocardiogram
EC	Ethics Committee
eCRF	electronic case report form
ED	exposure days
eDiary	electronic diary
eDMC	external Data Monitoring Committee
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EHC	European Haemophilia Consortium
ELISPOT	Enzyme-Linked Immune-Spot
EMA	European Medicines Agency
EOS	end of study
EQ-5D-5L	EuroQol, 5 dimensions, 5 levels
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FA	final analysis
FDA	U.S. Food and Drug Administration
FIX	coagulation factor IX
FII	coagulation factor II (or prothrombin)
FV	coagulation factor V
FVIII	coagulation factor VIII
FVIII:C	factor VIII: circulating
Gal3BP	Galectin-3 Binding Protein
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Grp78	78-kDa glucose-regulated protein
H2	histamine type 2
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL	high-density lipoprotein
hFVIII	human factor VIII
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HLA	human leukocyte antigen
HLIQ	Hemophilia Life Impacts Questionnaire
IA	interim analysis

Abbreviation	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	institutional ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-6	interleukin-6
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRR	infusion-related reaction
ISF	investigator site file
ITR	inverted terminal repeat
IV	intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDH	lactic acid dehydrogenase
LDL	low-density lipoprotein
LFT	liver function tests
LL	local laboratory
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MHC	major histocompatibility complex
mRNA	messenger ribonucleic acid
nAb	neutralizing antibodies
NE	non-evaluable
NHF	National Hemophilia Foundation
NHP	non-human primate
NI	noninferiority
NIMP	noninvestigational medicinal product
NSAIDs	nonsteroidal anti-inflammatory drugs
PA	primary analysis
PACL	protocol administrative change letter
PBMC	peripheral blood mononuclear cells
PCD	primary completion date
PCR	polymerase chain reaction
PGIC	Patient Global Impression of Change
PGIC-H	Patient Global Impression of Change - Hemophilia
PGIC-PF	Patient Global Impression of Change – Physical Functioning

Abbreviation	Definition
PGIC-PH	Patient Global Impression of Change – Physical Health
PGIS	Patient Global Impression of Severity
PGIS-H	Patient Global Impression of Severity – Haemophilia (PGIS-H
PGIS-PF	Patient Global Impression of Severity – Physical Functioning
PGIS-PH	Patient Global Impression of Severity – Physical Health
PK	pharmacokinetic
PPI	proton pump inhibitor
PRN	as needed
PROs	patient-reported outcomes
PT	prothombin
qPCR	quantitative real-time polymerase chain reaction
QTc	corrected QTc interval
rAAV	recombinant adeno-associated virus
rAAV6	recombinant adeno-associated virus serotype 2/6
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOC	standard of care
SUSAR	suspected unexpected serious adverse reactions
TAT	thrombin-antithrombin level
TBili	total bilirubin
TGA	thrombin generation assay
ULN	upper limit of normal
US	United States
vg/kg	vector genome per kilogram
VLDL	very-low-density lipoprotein
WBC	white blood cell
WFH	World Federation of Hemophilia

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