TITLE PAGE

Protocol Title: Phase 3, open label, single arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-Padua) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2)

Protocol Number: C0371002

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Compound Number: PF-06838435

Study Phase: Phase 3

Short Title: BeneGene-2

Acronym: Not applicable

Sponsor Name: Pfizer, Inc.

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA.

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Approval Date: 29 June 2022

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY		
Document	**Date**	**Summary and Rationale for Changes**
Amendment 3	**29 June 2022**	Pfizer has adjusted the position and ordering of endpoints to align with FDA recommendations (received 28 Mar 2022) which are in line with the changing landscape of gene therapy for hemophilia. The following revisions were made (Sections 1.1, 1.2, 2.2.2, 3, 4.2, 9.1, 9.4.1): • The primary endpoint was revised to ABR for total bleeds (treated and untreated). ABR for treated bleeds is now part of the key secondary endpoints. • Moved, "Vector-derived FIX:C level at steady-state (from Week 12 to 15 months) demonstrated to be greater than 5%," to key secondary endpoint and added, "FIX:C will also be summarized descriptively by study visit." • The assessment of all endpoints related to bleeds and infusions (including ABR for total bleeds, ABR for treated bleeds, AIR, FIX consumption, and annualized number of bleeding events of specific type) will start from Week 12 post-PF-06838435 infusion (instead of Day 1), corresponding to the estimated FIX:C steady state onset. • Re-ordered the sequence of secondary endpoints and added "Vector-derived FIX:C level by study visit and the geometric mean at each yearly interval" to secondary endpoints. Incorporated clarifications previously communicated by PACL #8 (Section 8.1.1): • What steps should be taken in the event of eDiary non-compliance. • What factor IX (FIX) treatment is required to be reported after Week 78 (Visit 14) for those participants who may have to resume FIX prophylaxis treatment. Updated sample size justification for ABR_{total}: • Section 9.2 Sample Size Determination Clarified that the definition of bleed refers to treated bleed:

DOCUMENT HISTORY		
Document	**Date**	**Summary and Rationale for Changes**
		• Section 10.7 Appendix 7: Bleed and Factor Replacement Regimen Definitions Updated rationale for NI margin selection for ABR_{total}: • Section 10.10 Appendix 10: Non-Inferiority Margin Selection Editorial, grammatical, formatting, and administrative changes were made throughout the document, including changes to the List of Abbreviations.
Editorial, grammatical, formatting, and administrative changes were made throughout the document.		

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/independent ethics committees (IECs).

TABLE OF CONTENTS

LIST OF TABLES 9
LIST OF FIGURES 9
1. PROTOCOL SUMMARY 10
1.1. Synopsis 10
1.2. Schema 12
1.3. Schedule of Activities (SoA) 13
2. INTRODUCTION 29
2.1. Study Rationale 31
2.2. Background 31
2.2.1. PF–06838435, Composition of the Vector 31
2.2.2. Summary of Clinical Experience with PF–06838435 32
2.3. Benefit/Risk Assessment 33
3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS 33
4. STUDY DESIGN 35
4.1. Overall Design 35
4.2. Scientific Rationale for Study Design 36
4.3. Justification for Dose 36
4.4. End of Study Definition 36
5. STUDY POPULATION 37
5.1. Inclusion Criteria 37
5.2. Exclusion Criteria 38
5.3. Lifestyle Considerations 40
5.4. Screen Failures 41
6. STUDY INTERVENTION 41
6.1. Study Intervention(s) Administered 41
6.2. Preparation/Handling/Storage/Accountability 42
6.3. Measures to Minimize Bias: Randomization and Blinding 42
6.4. Study Intervention Compliance 42
6.5. Concomitant Therapy 43
6.5.1. Allowed Therapy 44
6.5.2. Disallowed Therapy 45

6.6. Dose Modification 45
6.7. Intervention after the End of the Study 45
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 45
7.1. Discontinuation of Study Intervention 45
7.2. Participant Discontinuation/Withdrawal from the Study 46
7.2.1. Withdrawal of Consent 46
7.3. Lost to Follow up 47
8. STUDY ASSESSMENTS AND PROCEDURES 47
8.1. Efficacy Assessments 50
8.1.1. Hemophilic Bleeding Episodes and Treatment 50
8.1.2. Joint Assessments 51
8.1.2.1. Hemophilia Joint Health Score (HJHS) 51
8.1.2.2. Magnetic Resonance Imaging (MRI) to Evaluate Joints 51
8.1.2.3. X–ray Assessments to Evaluate Joints 52
8.1.3. Patient–Reported Outcomes (PROs) 52
8.1.3.1. Haemophilia Quality of Life Questionnaire for Adults (Haem–A–QoL) 53
8.1.3.2. Hemophilia Activities List (HAL, Version 2) 53
8.1.3.3. Patient Global Impression of Change – Hemophilia (PGIC–H) 53
8.1.3.4. Hemophilia Life Impacts Questionnaire (HLIQ) 53
8.1.3.5. EQ–5D–5L 54
8.2. Safety Assessments 54
8.2.1. Physical Examinations 54
8.2.2. Vital Signs 54
8.2.3. Electrocardiograms 54
8.2.4. Clinical Laboratory Assessments 54
8.2.5. Liver Ultrasound 55
8.3. Adverse Events and Serious Adverse Events 55
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 56
8.3.1.1. Reporting SAEs to Pfizer Safety 57
8.3.1.2. Recording Non-serious AEs and SAEs on the CRF 57

8.3.2. Method of Detecting AEs and SAEs 57
8.3.3. Follow–up of AEs and SAEs 57
8.3.4. Regulatory Reporting Requirements for SAEs 58
8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure 58
8.3.5.1. Exposure During Pregnancy 58
8.3.5.2. Exposure During Breastfeeding 60
8.3.5.3. Occupational Exposure 60
8.3.6. Immunogenicity 60
8.3.6.1. Analysis of Anti– PF–06838435 Antibodies and Neutralizing Anti PF–06838435 Antibodies 60
8.3.6.2. Analysis of FIX Inhibitor 61
8.3.6.3. Analysis of Cellular Immune Response by ELISPOT (enzyme–linked immuno–spot) 61
8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs 62
8.3.8. Immunomodulation Optimization (Presumed T-Cell Activation) 62
8.3.9. Adverse Events of Special Interest 66
8.3.9.1. Lack of Efficacy 66
8.3.10. Thrombotic Potential Assessments (ONLY for participants who reach vector-derived FIX:C Activity Levels >150% After the Infusion of PF–06838435) 66
8.3.11. Medication Errors 66
8.4. Treatment of Overdose 67
8.5. Pharmacokinetics 67
8.5.1. Samples for Vector Shedding Assays 68
8.6. Pharmacodynamics 68
8.6.1. Samples for FIX Antigen Levels 69
8.6.2. Samples for Thrombin Generation 69
8.6.3. Samples for D-dimer 69
8.6.4. Shipment of Pharmacodynamic Samples 69
8.7. Genetics 69
8.7.1. Specified Genetics 69
8.7.2. Banked Biospecimens for Genetics 70

8.8. Biomarkers 70
8.9. Health Economics 70
9. STATISTICAL CONSIDERATIONS 70
9.1. Estimands and Statistical Hypotheses 70
9.1.1. Estimands 70
9.2. Sample Size Determination 71
9.3. Populations for Analyses 71
9.4. Statistical Analyses 71
9.4.1. Efficacy Analyses 72
9.4.2. Safety Analyses 74
9.4.3. Other Analyses 74
9.5. Interim Analyses 74
9.5.1. External Data Monitoring Committee (eDMC) 74
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 75
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 75
10.1.1. Regulatory and Ethical Considerations 75
10.1.2. Financial Disclosure 76
10.1.3. Informed Consent Process 76
10.1.4. Data Protection 77
10.1.5. Committees Structure 78
10.1.6. Dissemination of Clinical Study Data 78
10.1.7. Data Quality Assurance 79
10.1.8. Source Documents 81
10.1.9. Study and Site Closure 81
10.1.10. Publication Policy 81
10.1.11. Sponsor's Qualified Medical Personnel 82
10.2. Appendix 2: Clinical Laboratory Tests 83
10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow–up, and Reporting 85
10.3.1. Definition of AE 85
10.3.2. Definition of SAE 86
10.3.3. Recording and Follow–Up of AE and/or SAE 89

10.3.4. Reporting of SAEs 92
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information 94
10.5. Appendix 5: Genetics 95
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments 96
10.7. Appendix 7: Bleed and Factor Replacement Regimen Definitions 98
10.8. Appendix 8: Guidelines for Target Factor IX Levels Based on Bleed Type 100
10.9. Appendix 9: Instruments for Patient-Reported Outcomes (PROs) 101
10.9.1. Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) 101
10.9.2. Hemophilia Activities List (HAL) 108
10.9.3. Patient Global Impression of Change - Hemophilia (PGIC-H) 116
10.9.4. Hemophilia Life Impacts Questionnaire (HLIQ) 117
10.9.5. EQ-5D-5L Questionnaire 121
10.10. Appendix 10: Non-Inferiority Margin Selection 124
10.11. Appendix 11: Country-specific Requirements 126
10.11.1. Japan Appendix 126
10.11.1.1. Study Intervention Defects Definitions (per Japanese regulations) 126
10.11.1.2. Reporting Criteria 126
10.11.1.3. Reporting Procedures 126
10.11.1.4. Japan Specific Protocol Wording 127
10.11.2. Germany Appendix 127
10.11.2.1. Section 5.1 Inclusion Criteria 128
10.11.2.2. Section 5.2 Exclusion Criteria 128
10.11.2.3. Section 10.1.3. Informed Consent Process 128
10.11.2.4. Section 1.3. Schedule of Activities (SoA) 128
10.11.2.5. Section 8.1.2.3. X-ray Assessments to Evaluate Joints 128
10.12. Appendix 12: Hemophilia Joint Health Score 129
10.13. Appendix 13: Alternative Measures During Public Emergencies 131
10.13.1. Alternative Study Procedures During COVID-19 Pandemic 131
10.13.1.1. Home Health Visits 131
10.13.1.2. Telehealth Visits 131

10.13.1.3. Guidelines for Capturing Post-Infusion Procedures.....132
10.13.2. Alternative Study Procedures For Extenuating Circumstances.....132
10.13.3. Participants Who Test Positive for COVID-19 132
10.13.4. COVID-19 Vaccination Guidelines.....133
10.14. Appendix 14: Protocol Amendment History.....134
10.15. Appendix 15: Abbreviations 145
11. REFERENCE.....149

LIST OF TABLES

Table 1. Recommended Regimen for Oral Corticosteroids.....64
Table 2. Recommended Regimen for Combination Intravenous and Oral Corticosteroids.....65

LIST OF FIGURES

Figure 1. C0371002: Study Schematic.....12
Figure 2. Schematic of PF-06838435 Vector Genome 32

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Phase 3, open label, single arm study to evaluate efficacy and safety of FIX gene transfer with PF-06838435 (rAAV-Spark100-hFIX-Padua) in adult male participants with moderately severe to severe hemophilia B (FIX:C ≤2%) (BeneGene-2)

Short Title: BeneGene-2

Rationale:

The published data from the Phase 1/2a study for PF-06838435 (SPK-9001-101) indicate that treatment of hemophilia B with PF-06838435 offers considerable clinical advantage over routine prophylactic treatment with factor IX (FIX) product. A single infusion of PF-06838435 results in sustained FIX activity levels in the mild to normal range with associated low bleeding rates and a marked reduction in the number of infusions of FIX product (see Section 2.2.2). This Phase 3 confirmatory study will compare the efficacy of PF-06838435 treatment with routine prophylaxis with the objective to establish non-inferiority and possibly superiority.

Objectives, Estimands and Endpoints

The primary objective is addressed via the primary endpoint of annualized bleeding rate (ABR) for total bleeds (treated and untreated) (referred to as ABR_{total} thereafter in this document). Efficacy by ABR_{total} is summarized by the difference between pre- and post-treatment with PF-06838435; pre-treatment data will be obtained from the lead-in study (C0371004) as well as during the period prior to study drug infusion in Study C0371002 (referred to as "Pre-Infusion Period" thereafter in this document). Steady-state circulating FIX (FIX:C) is a key secondary endpoint and the efficacy by FIX:C is summarized by the steady-state population mean post-treatment compared to a fixed threshold of 5%. Since no more than the single dose of study treatment on Day 1 will be administered during the study, there should be no treatment discontinuations. Resumption of FIX prophylaxis regimen is allowed as detailed in Section 6.5.1and is assessed directly via secondary endpoints (annualized (FIX) infusion rate [AIR] and FIX consumption). Data following resumption of FIX prophylaxis regimen will not be included in the primary analysis of ABR_{total}. There may be missing data from participants lost to follow-up, but it is anticipated to be rare. The primary endpoint, ABR_{total}, will utilize all applicable data to define the endpoint. Any missing data will not be imputed for the primary endpoint. The method to handle missing data of other endpoints will be discussed in the Statistical Analysis Plan (SAP). Baseline for change from baseline analyses will be defined based on the data collection method of each endpoint, but will reflect data before PF-06838435 (also referred to as IP) infusion.

Primary Objectives	Primary Endpoints
To demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).	Primary endpoint: • Non-inferiority on annualized bleeding rate (ABR) for total bleeds (treated and untreated) from Week 12 to Month 15 versus standard of care (SOC) FIX prophylaxis replacement regimen, comparing pre-and post-IP infusion.
Secondary Objectives	**Secondary Endpoints**
Key secondary objectives: To demonstrate the efficacy of PF-06838435 in terms of the use of exogenous FIX, the treated bleeds, and FIX:C.	• Key secondary endpoints: o Non-inferiority on ABR for treated bleeds from Week 12 to Month 15 versus SOC FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion. o Annualized infusion rate (AIR) of exogenous FIX from Week 12 to Month 15 versus AIR of FIX with SOC FIX replacement regimen pre-IP infusion. o Vector-derived FIX:C level at steady state (from Week 12 to 15 months) demonstrated to be greater than 5%. FIX:C will also be summarized descriptively by study visit.

Overall Design:

This Phase 3, open-label, single arm, multi-site study will compare the efficacy of a single intravenous (IV) infusion of PF-06838435 with routine FIX prophylaxis, in adult male participants from the lead-in study (C0371004) with severe to moderately severe hemophilia B (≤2%). Eligible study participants will have completed a minimum 6 months of routine FIX prophylaxis therapy during the lead-in study (C0371004). The study duration for each participant in this study will be 312 weeks (see Section 1.3 for SoA). At least 50 participants will be screened to dose at least 40 participants with PF-06838435, and all 40 participants are expected to be evaluable.

Disclosure Statement:

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

Number of Participants:

Approximately 50 participants will be screened to achieve 40 participants assigned to study intervention for an estimated total of 40 evaluable participants.

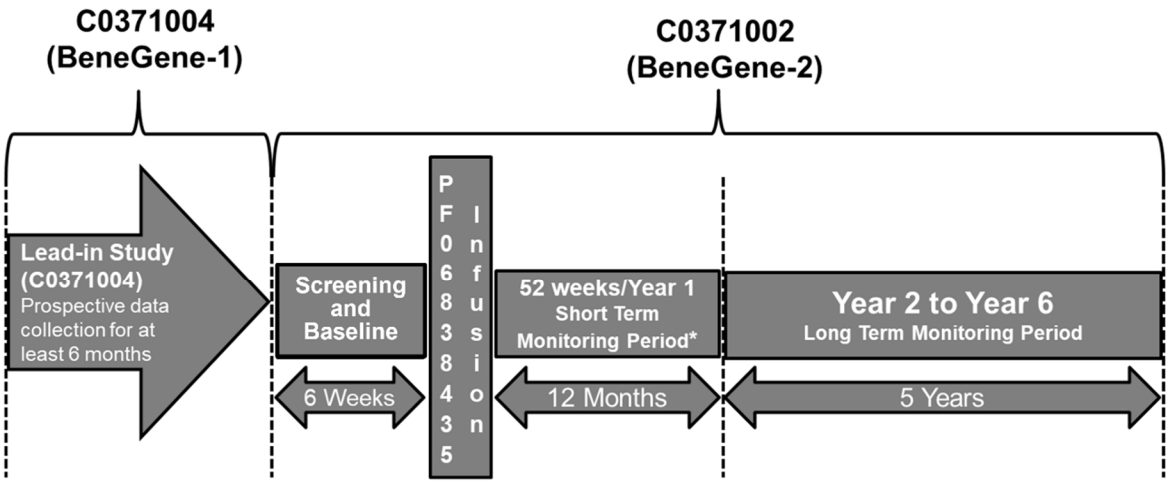
Intervention Groups and Duration:

The study treatment, a single infusion of PF-06838435, a gene transfer agent, will be administered on Day 1 at a dose of 5×10^{11} vector genomes/kg of body weight. The safety and efficacy data will be collected over 6 years as per the SoA included in Section 1.3.

Data Monitoring Committee: Yes

1.2. Schema

Figure 1. C0371002: Study Schematic



* Primary endpoint ABR for total bleeds, as well as key secondary endpoints of AIR, ABR for treated bleeds, and FIX:C will be analyzed from Week 12 to Month 15.

1.3. Schedule of Activities (SoA)

Alternative study measures during the COVID-19 Pandemic and for Extenuating Circumstances is described in Appendix 13.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	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 from participants prior to 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	X*		X#											* Review and confirm eligibility criteria (see Sections 5.1 & 5.2). This needs to be completed prior to ordering IP at the beginning of the Baseline Period. # Review and confirm eligibility (see Sections 5.1 & 5.2) prior to infusion (Infusion Center should confirm eligibility with study site).
Demographics, Medical, Surgical, and Hemophilia History (including vaccination history)	X													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. Only changes to historical data on Demographics, 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**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Physical Exam, Weight, and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	Complete Physical Exam at all clinic visits (Height is required to be collected at Screening Visit). Weight must be obtained at Screening Visit to order the correct quantity of IP. Weight at Screening Visit (Visit 1) will be used to calculate the dose (Section 8.2.1). **Vital signs include**: body temperature (°C) (see Section 8.2.2), BP, pulse rate, respiratory rate, after at least 5 mins rest in supine or upright/sitting position. Vital signs are to be measured as specified below. **Vital signs (at Day 1)** will be obtained: • prior to **FIX infusion**; • 30±2 mins **after the start of IP infusion (taken during infusion)**; • approximately 2 mins, 2 hrs ±10 mins, 6 hrs ±10 mins, and 24 (±3) hrs **after completion of IP infusion and IV line flush**.
Electrocardiogram	X												X	12-lead ECG will be obtained for the study. Additional ECGs may be obtained as clinically indicated.
Target Joint Assessment	X													See Appendix 7 for definition of a target joint. Done as part of hemophilia history.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					**•The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** •The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. •After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. •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. •Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. •*Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. •Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. •Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. •Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Joint X-ray		X*#												*Some participants (n~40), who consent to participate in an optional sub-study, will undergo X-ray for assessment of joints (Section 8.1.2.3). For German sites please refer to Germany Appendix (Section 10.11.2.4). # If this X-ray can't be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4/ Visit 6.
Joint MRI		X*#												*Some participants (n~20), who consent to participate in an optional sub-study, will undergo joint MRIs (Section 8.1.2.2). # If this MRI can't be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4/ Visit 6.
HBcAB, HCV, CD4, human immunodeficiency virus (HIV) Serology, Liver fibrosis testing & Urinalysis (CL*)	X													Hepatitis: HBsAg, HBcAb, HBV-deoxyribonucleic acid (DNA); HCV-RNA Quantitative Liver fibrosis: FibroScan, FibroTest/FibroSURE, or AST to platelet ratio index (APRI). * FibroScan, if performed, would be performed locally. HIV: Antibody testing, and CD4 count/HIV viral load (if antibody positive). Urinalysis: pH, specific gravity, protein, blood, ketones, glucose.
α-Fetoprotein (CL)	X												X	To be tested as biomarker for hepatic carcinoma.
FIX genetic testing (CL)	X*													*Test to be performed if results are not available in the source documents.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
FIX Inhibitor testing (CL, test in LL if clinically necessary)	X*				X	X	X	X	X	X	X	X	X	**These specimens should be collected in the absence of residual infused FIX.** *Positive inhibitor testing as measured by the central laboratory ≥0.6 Bethesda Units (BU) at Visit 1 would be exclusionary. Nijmegen Bethesda Inhibitor assay at the central lab unless testing at a local lab is necessary due to a clinical concern.
nAb Assay to adeno-associated virus (AAV)-Spark 100 (CL)	X*												X	*Participants with Anti-AAV-Spark100 neutralizing antibodies (nAb) titer ≥ 1:1 (ie, positive for nAb) are to be excluded from the study.
Anti-Drug Antibody/ADA (CL)	X												X	Anti-PF-06838435 antibodies (ADA) from human serum.
Laboratory Safety Panels (Hematology and Clinical Chemistry) (CL)	X				X	X	X	X	X	X	X	X	X	• Hematology: WBC and differential, RBC, hemoglobin, hematocrit, and platelet count. • ABO blood group (CL) (at Screening if unknown). • Chemistry: Na, K, Cl, phosphate, bicarbonate, glucose, BUN, serum creatinine.
Laboratory Safety Panels (Lipid Panel) (CL)	X												X	These specimens are to be drawn after at least 8 hours of fasting (Appendix 2).

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
FIX Activity, LFT (CL, LL) and FIX Antigen (CL)*	X			Collect 2-3 times every week starting from Day 1. Utilize mobile phlebotomy/ home health services as needed.					Week 13 to Week 18: Collect once every week. Utilize mobile phlebotomy/ home health services as needed. Week 19 to Week 52: Collect at site visits.					• LFT: albumin, total bilirubin, direct bilirubin, indirect bilirubin (if available), ALP, AST, ALT, total protein, GGT, LDH. • FIX:C, FIX Ag. • **FIX Activity should be collected in the absence of residual infused FIX.** • For first 12 weeks, 2 or 3 times every week monitoring will be conducted due to potential rise in hepatic transaminases and/or loss of FIX transgene expression. • Sponsor recommends collecting specimens on Mondays through Thursdays so that the results are available prior to the weekend. • *** FIX Activity and LFT testing will be conducted at local AND central lab for all time points and as clinically necessary (including samples drawn at the clinic and any mobile phlebotomy/ home health service visits)**. FIX Antigen testing will be conducted ONLY at central lab for all time points and as clinically necessary. Clinical decisions may be based on local and/ or central lab results.
Order the IP		X												IP is to be ordered at the beginning of the Baseline Period after confirming eligibility criteria. The IP will take approximately 3 weeks for delivery. Prior to ordering IP, Sections 10.13.3 and 10.13.4 should be considered.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					**•The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** •The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. •After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. •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. •Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. •*Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. •Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. •Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. •Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Immunology (PBMC) (CL)		X		Only if corticosteroid treatment is needed for a suspected T-cell response. Utilize mobile phlebotomy/ home health services as needed and if possible.										•Specimens for PBMC by ELISPOT are to be collected at Baseline and if the corticosteroid treatment is needed for a suspected T-cell response. •Specimens are to be collected prior to initiating the corticosteroid treatment. If not collected prior to initiation, specimens must be collected within 24 hours of administering corticosteroids. •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, ranitidine) for the duration of the corticosteroid course. •Specimens are to be collected approximately 3 weeks after steroid administration. Additional specimens may be necessary if ELISPOT has not normalized at 3 weeks and/or based on medical judgement.
Immunology Exploratory (PBMC) (CL)	X				X	X	X	X					X	Utilize mobile phlebotomy/ home health services, as needed and if possible. Collect blood for PBMC preparation for cell-mediated exploratory immunology assays.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Immunology - Exploratory (binding IgG vs IgM antibody response) (CL)		X		X*	X									Serum samples will be used for these tests. Post-dose samples will be collected on Week 1 and Week 2. *Specimen is required at Visit 4 and can be obtained via mobile phlebotomy/ home health service.
Spare Plasma	X	X	X	X	X	X	X	X	X	X	X	X	X	Approximately 5 mL of blood will be drawn to provide approximately 2 mL of plasma, each time blood is collected for central laboratory samples. The plasma will be stored for repeat or additional testing. These samples will be destroyed at the end of the study.
Liver Ultrasound	X												X	All participants will undergo liver ultrasound. Imaging will be performed locally (Section 8.2.5).
Global Hemostasis Markers (CL)	X												X	aPTT (in seconds), INR, TAT, TGA, and D-dimer, **These specimens should be collected in the absence of residual infused FIX**. The tests may be conducted as clinically indicated throughout the study.
Issue the eDiary	X													Provide eDiary and training to operate it, including timing and information to be entered starting at Visit 1 (see Section 8.1.1).
Review the eDiary		Ongoing (including unscheduled visits)#												Review the eDiary data (see Section 8.1.1), ensure appropriate entries, during unscheduled and scheduled visits. # Infusion centers are not required to perform this activity on Visit 3; however, the study site is required to perform this review.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • ∗Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Pre-Dosing LFTs			X											Blood for LFTs are to be drawn and tested locally and centrally prior to dosing participants (up to 3 days prior to Day 1/ Visit 3 is acceptable). Utilize mobile phlebotomy/ home health services as needed, and if possible. Local LFTs are required to be reviewed 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. These LFT results should be entered into the CRF as an unplanned visit.
FIX Infusion, Accountability			X											On Day 1 a single prophylactic IV infusion of a FIX product will be administered under medical supervision, over a period of approximately 10 minutes at a dose of 100 IU/kg for standard half-life products and 50 IU/kg for extended half-life products**, within reasonable margin of error (approximately ±20%)**. If there is evidence to show that these doses may place the participant at supratherapeutic FIX levels, the dose can be adjusted. Participants are expected to bring their current Factor IX replacement therapy with them.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
IP Infusion, Accountability			X											Prior to dosing, Section 10.13.3 and 10.13.4 should be considered. After the completion of FIX product infuion, participants will receive a single IV infusion of the IP over approximately 60 minutes via infusion pump. IP should NOT be thawed without: confirmation of eligibility, Pre-Dosing LFT results, AND affirming that the participant is physically present at the study site (or infusion center). **The IV line should be flushed at the conclusion of the IP infusion.**
HJHS		X								X			X	To be completed by investigator or the designee (Section 8.1.2.1).
Patient-Reported Outcomes (PROs)		X*						X		X			X	Participants will complete 5 instruments at the site using an electronic tablet: Haem-A-QoL, Haemophilia Activities List [HAL (v2)], PGIC-H, HLIQ, and EQ-5D-5L. The questionnaires should be administered before dosing, treatment, or conversation between health care team and participants about their health condition. See Section 8.1.3 for additional considerations. * PGIC-H is not completed at baseline visit. Every effort should be made to conduct the PROs according to the protocol specified timepoints, especially the baseline visit. Baseline PRO assessments need to be done prior to start of infusion on Day 1 if not done at baseline visit. If the post-infusion PROs can't be performed at a particular visit, they should be performed at the next visit.

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					**•The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** •The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. •After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. •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. •Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. •*Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. •Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. •Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. •Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Vector Shedding Analysis by PCR (CL)		X	X*	Weekly, as needed# Utilize mobile phlebotomy / home health services, as needed										•# Plasma, PBMC, saliva, semen, and urine specimens will be collected at baseline and every week after IP administration until 3 consecutive specimens test negative for the given specimen type. •Semen samples can be collected at home the night before a clinic or mobile phlebotomy/ home health service visit and stored in the participant's freezer until the clinic or mobile phlebotomy/ home health service visit, with the exception of semen samples collected as part of the optional vector shedding sub-study (see bullet point below) •*Optional Vector Shedding Sub-study: Additional (2 hrs (±30 minutes), 24 hrs (±3 hrs), 72 hrs (±4 hrs) after completion of IP infusion and IV line flush on Day 1) samples (plasma, PBMC, saliva, semen, and urine) will be collected from some participants (n=12) who consent to participate in an optional sub-study. Utilize mobile phlebotomy/ home health services as needed.
Any Additional Safety Tests	Ongoing (as needed)													Additional laboratory testing 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 52 weeks post-infusion) all SAEs and AEs (including medically important events) will be collected (Appendix 3).

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**					• **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.** • The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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. • After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1. • 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. • Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed. • *Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA. • Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required. • Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13	
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52	
Concomitant Medications, Surgeries, and Procedures	Ongoing (including unscheduled visits)													All concomitant therapy 30 days prior to Screening, during Screening and Short-Term Monitoring Period will be recorded up to and including 52 weeks post-infusion as per Section 6.5. All procedures and surgeries (including elective surgeries) during the Screening and Short-Term Monitoring Period are to be recorded.

Note: Study Site: Will screen and follow study participants post-infusion of PF-06838435 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-06838435.

AAV: adeno-associated virus; ADA: Anti-drug antibody; AE: adverse event; ALP: alkaline phosphatase; ALT: alanine transaminase; APRI: AST to Platelet Ratio Index; aPTT: activated partial thromboplastin time, AST: aspartate transaminase; BUN: blood urea nitrogen; CBC: complete blood count; CD4: cluster of differentiation or classification determinant; CL: central laboratory; CPT: cell preparation tube; Cr: creatinine; DNA: deoxyribonucleic acid; ECG: electrocardiogram; ELISPOT: Enzyme-Linked ImmunoSpot assay; EOS: End of Study; EQ-5D-5L: EuroQol, 5 dimensions, 5 levels; FIX: coagulation factor IX; FIX Ag: factor IX antigen; FIX:C: circulating FIX; HBcAb: Hepatitis B core antibody; GGT: gamma-glutamyl transferase; 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; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HJHS: hemophilia joint health score; HLIQ: Hemophilia Life Impacts Questionnaire; ICF: Informed Consent Form; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: international normalized ratio; IP: investigational product; IU: international units; K: potassium; LDH: lactic acid dehydrogenase; LFT: liver function tests; LL: local laboratory; mins: minutes; MRI: magnetic resonance imaging; n: number; Na: sodium; nAb: neutralizing antibodies; PBMC: peripheral blood mononuclear cells; PCR: polymerase chain reaction; PGIC-H: Patient Global Impression of

Procedures Year 1	**Screening Period**	**Baseline Period**	**IP Infusion**	**Week 1-12 (± 2 days)**					**Week 13-52 (±1 week)**				
Study Visit	1	2	3	4*	5	6	7	8	9	10	11	12	13
Weeks after IP administration The schedule of assessments should be based on Day 1	Week -6 to Week -3	Week -3 to Day 1	Day 1	1	2	4	8	12	18	24	32	42	52

- **The following Screening labs should be collected in the absence of residual infused FIX (FIX trough): FIX activity, hemostasis markers, inhibitor testing.**
- The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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.
- After determination of eligibility, FIX replacement therapy and IP Infusion will be planned at a time when a routine FIX infusion will occur during the study visit on Day 1.
- 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.
- Day 1: All eligible participants will be dosed on Day 1 and are required to return to the infusion center or study site 24 hours after being dosed (on Day 2) to have their vital signs assessed.
- ∗Visit 4: The participant is not required to appear in person at this visit. Visit 4 study procedures are not required to be performed if the participant does not appear in person with the exception of all required laboratory specimens (eg, Immunology – Exploratory [IgG vs IgM antibody response], Vector Shedding Analysis by PCR, FIX Activity, Antigen and LFT) which can be obtained via mobile phlebotomy home health services. If participants physically attend this visit, all procedures are to be performed per SOA.
- Unscheduled visits may be necessary during the study for safety monitoring or to repeat any blood sampling if required.
- Mobile phlebotomy/home health services may be utilized for Pre-Dose LFT blood draws and most blood collections after Study Day 1/Visit 3 infusion, as needed. Additionally, mobile phlebotomy/home health service may be utilized, prior to Visit 3, upon sponsor approval, except for pre-dose LFT blood draws which do not require sponsor approval.
- Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.

Change- Hemophilia; PROs: patient-reported outcomes; RNA: ribonucleic acid; SAE: serious adverse event; TAT: thrombin-antithrombin level; TGA: Thrombin generation assay; vg: vector genome; WBC: white blood cell.

Alternative study measures during the COVID-19 Pandemic and for Extenuating Circumstances is described in Appendix 13.

Procedures Year 2 to Year 6	**Week 53-156 (±2 weeks)**				**Week 157-260 (±3 weeks)**		**EOS Week 312 (±3 weeks)**	• Unscheduled visits may be necessary during the study. Tests being performed are for safety monitoring purposes, for repeat safety assessments, or to repeat any blood sampling if required. • During Long-Term Monitoring Period (Weeks 53 to 312), mobile phlebotomy/ home health services may be utilized as needed, when site visits are not scheduled. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Weeks after IP administration	**78**	**104**	**130**	**156**	**208**	**260**	**312**	
Physical Exam, Weight, and Vital Signs	X	X	X	X	X	X	X	Complete Physical Exam at all visits. Vital signs include: body temperature (°C) (see Section 8.2.2), BP, pulse rate, respiratory rate, after at least 5 mins rest in supine or upright/sitting position.
Electrocardiogram	As needed							12-lead ECG will be obtained for the study. Additional ECGs may be obtained as clinically indicated.
Joint X-ray				X*,#			X*,#	*Some participants (n~40), who consent to participate in an optional sub-study, will undergo X-ray for assessment of joints (Section 8.1.2.3). For German sites please refer to Germany Appendix (Section 10.11.2.4). # If the baseline X-ray could not be performed ≤ Week 4/ Visit 6, the study participant does not need to do the 3 (Visit 17) and 6 year (Visit 20) follow-up X-rays.
Joint MRI				X*,#			X*,#	*Some participants (n~20**)**, who consent to participate in an optional sub-study, will undergo joint MRIs (Section 8.1.2.2). # If the baseline MRI could not be performed ≤ Week 4/ Visit 6, the study participant does not need to do the 3 (Visit 17) and 6 (Visit 20) year follow-up MRIs.
α-Fetoprotein (CL)	X	X	X	X	X	X	X	To be tested as biomarker for hepatic carcinoma.
FIX Inhibitor Testing (CL, test in LL if clinically necessary)	X	X	X	X	X	X	X	Nijmegen Bethesda Inhibitor Assay: At central laboratory; local laboratory allowed if required for clinical reasons. **These specimens should be collected in the absence of residual infused FIX.**
nAb Assay to AAV Spark 100 (CL)		X		X	X	X	X	
Anti-Drug Antibody/ADA (CL)				X			X	Whole blood will be collected for determination of anti-PF-06838435 antibodies (ADA) from human serum.
Laboratory Safety Panels (Hematology and Clinical Chemistry) (CL)	X	X	X	X	X	X	X	• Hematology: WBC and differential, RBC, hemoglobin, hematocrit, and platelet count • Chemistry: Na, K, Cl, phosphate, bicarbonate, glucose, BUN, serum creatinine.

Procedures Year 2 to Year 6	**Week 53-156 (±2 weeks)**				**Week 157-260 (±3 weeks)**		**EOS Week 312 (±3 weeks)**	• Unscheduled visits may be necessary during the study. Tests being performed are for safety monitoring purposes, for repeat safety assessments, or to repeat any blood sampling if required. • During Long-Term Monitoring Period (Weeks 53 to 312), mobile phlebotomy/ home health services may be utilized as needed, when site visits are not scheduled. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Weeks after IP administration	**78**	**104**	**130**	**156**	**208**	**260**	**312**	
FIX Activity, LFT (CL, LL) and FIX Antigen (CL)*	Starting at Week 53, monitor <u>once every 3 months$</u>				Starting at Week 157, monitor <u>once every 6 months#</u>		X	• LFT: albumin, total bilirubin, direct bilirubin, indirect bilirubin (if available), ALP, AST, ALT, total protein, GGT, LDH. • FIX:C, FIX Ag. • **FIX Activity should be collected in the absence of residual infused FIX** • Sponsor recommends collecting specimens on Mondays through Thursdays so that the results are available prior to the weekend. • *** FIX Activity and LFT testing will be conducted at local AND central lab for all time points and as clinically necessary (including samples drawn at the clinic and any mobile phlebotomy/ home health service visits)**. FIX Antigen testing will be conducted ONLY at central lab for all time points and as clinically necessary. 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 (Visit 16), 143, 156 (Visit 17). • # Samples should be taken at weeks: 182, 208 (Visit 18), 234, 260 (Visit 19) and 286. • Utilize mobile phlebotomy/ home health services as needed.
Immunology (PBMC) (CL)	Only if corticosteroid treatment is needed for a suspected T-cell response. Utilize mobile phlebotomy/ home health services, as needed and if possible.						X	• Specimens for PBMC by ELISPOT are to be collected at End of Study and if the corticosteroid treatment is needed for a suspected T-cell response. • Specimens are to be collected prior to initiating the corticosteroid treatment. If not collected prior to initiation, specimens must be collected within 24 hours of administering corticosteroids. • 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, ranitidine) for the duration of the corticosteroid course. • Specimens are to be collected approximately 3 weeks after steroid administration. Additional specimens may be necessary if ELISPOT has not normalized at 3 weeks and/or based on medical judgement.
Spare Plasma	X	X	X	X	X	X	X	Approximately 5 mL of blood will be drawn to provide approximately 2 mL of plasma, each time blood is collected for central laboratory samples. The plasma will be stored for repeat or additional testing. These samples will be destroyed at the end of the study.
Liver Ultrasound		X		X	X	X	X	All participants will undergo liver ultrasound. Imaging will be performed locally (Section 8.2.5).
Global Hemostasis Markers (CL)		X		X	X	X	X	aPTT (in seconds), INR, TAT, TGA, and D-dimer. **These specimens should be collected in the absence of residual infused FIX**. The tests may be conducted as clinically indicated throughout the study.
HJHS		X		X	X	X	X	To be completed by the investigator or the designee (Section 8.1.2.1).

Procedures Year 2 to Year 6	**Week 53-156 (±2 weeks)**				**Week 157-260 (±3 weeks)**		**EOS Week 312 (±3 weeks)**	• Unscheduled visits may be necessary during the study. Tests being performed are for safety monitoring purposes, for repeat safety assessments, or to repeat any blood sampling if required. • During Long-Term Monitoring Period (Weeks 53 to 312), mobile phlebotomy/ home health services may be utilized as needed, when site visits are not scheduled. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Weeks after IP administration	**78**	**104**	**130**	**156**	**208**	**260**	**312**	
Patient-Reported Outcomes (PROs)		X		X	X	X	X	Participants will complete 5 instruments at the study site using an electronic tablet: Haem-A-QoL, HAL (v2), PGIC-H, HLIQ, and EQ-5D-5L. The questionnaires should be administered before dosing, treatment, or conversation between health care team and participants about their health condition. See Section 8.1.3 for additional considerations. Every effort should be made to conduct the PROs according to the protocol specified timepoints. If the post-infusion PROs can't be performed at a particular visit, they should be performed at the next visit.
Phone call					Ongoing			After Week 156, phone calls every 6 months (ie, weeks: 182, 234, 286) in addition to the annual visits. Inquire about AEs and concomitant treatments (including surgeries and procedures).
Vector Shedding Analysis by PCR (CL)	Weekly, as needed# Utilize mobile phlebotomy/ home health services as needed							• # Plasma, PBMC, saliva, semen, and urine: Specimens will be collected at baseline and every week after IP administration until 3 consecutive specimen test negative for the given specimen type. • Semen samples can be collected at home the night before a clinic or mobile phlebotomy/ home health service visit and stored in the participant's freezer until the clinic or mobile phlebotomy/ home health service visit.
Any Additional Safety Tests	Ongoing							Additional laboratory testing may be conducted as deemed clinically necessary by the investigator to ensure safety of participants.
Adverse Events	Ongoing (including unscheduled visits)							During the Long-Term Monitoring Period (Week 53 post-infusion to EOS) the following adverse events will be collected: • SAEs (including medically important events, Appendix 3). • Non-serious AEs determined to be related to IP by the investigator or where causality is unknown.
Concomitant Medications, Surgeries, and Procedures	Ongoing (including unscheduled visits)							During the Long-Term Monitoring Period (Week 53 post-infusion to EOS) the concomitant therapy associated with: SAEs (including medically important events, Appendix 3) Non-serious AEs determined to be related to IP by the investigator or where causality is unknown. All procedures and surgeries (including elective surgeries) during the Long-Term Monitoring Period are to be recorded.
Review of the eDiary	Ongoing (including unscheduled visits)							Review the eDiary; ensure appropriate entries, during unscheduled and scheduled visits.
Return eDiary							X	The eDiary will be returned during the Week 312 visit.

Study Site: Site that will screen and follow participant post-infusion of PF-06838435 for the duration of the study.
AAV: adeno-associated virus; ADA: Anti-drug antibody; AE: adverse event; ALP: alkaline phosphatase; ALT: alanine transaminase; APRI: AST to Platelet Ratio Index; aPTT: activated partial thromboplastin time, AST: aspartate transaminase; BUN: blood urea nitrogen; CBC: complete blood count; CL: central laboratory; CPT: cell preparation tube; Cr: creatinine; DNA: deoxyribonucleic acid; ELISPOT: Enzyme-Linked ImmunoSpot assay; EOS: End of Study; EQ-5D-5L: EuroQol, 5 dimensions, 3 levels; FIX: coagulation factor IX; FIX Ag: factor IX antigen; HBcAb: Hepatitis B core antibody; GGT: gamma-glutamyl transferase; Haem-A-QoL: Haemophilia Quality of Life Questionnaire for Adults; HAL: Haemophilia Activities List; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HJHS: hemophilia joint health score; HLIQ: Hemophilia Life Impacts Questionnaire; ICF: Informed Consent Form; INR: international normalized ratio; IP: investigational product; IU: international

Procedures Year 2 to Year 6	**Week 53-156 (±2 weeks)**				**Week 157-260 (±3 weeks)**		**EOS Week 312 (±3 weeks)**	• Unscheduled visits may be necessary during the study. Tests being performed are for safety monitoring purposes, for repeat safety assessments, or to repeat any blood sampling if required. • During Long-Term Monitoring Period (Weeks 53 to 312), mobile phlebotomy/ home health services may be utilized as needed, when site visits are not scheduled. • Early discontinuation visit should follow the procedures for Week 312 visit. The management of the participant and the risks inherent with discontinuation from the study should be discussed with the sponsor's medical monitor.
Study Visit	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Weeks after IP administration	**78**	**104**	**130**	**156**	**208**	**260**	**312**	

units; LDH: lactic acid dehydrogenase; LFT: liver function tests; LL: local laboratory; mins: minutes; MRI: magnetic resonance imaging; nAb: neutralizing antibodies; PBMC: peripheral blood mononuclear cells; PGIC-H: Patient Global Impression of Change- Hemophilia; PROs: patient-reported outcomes; RNA: ribonucleic acid; SAE: serious adverse event; TAT: thrombin-antithrombin level; TGA: Thrombin generation assay; vg: vector genome; WBC: white blood cell.

2. INTRODUCTION

PF-06838435 (generic name: fidanacogene elaparvovec; formerly known as SPK-9001 or rAAV Spark100-hFIX-Padua) is an adeno-associated viral (AAV) vector designed to drive expression of the human factor IX-Padua (hFIX-Padua) transgene and raise the circulating levels of FIX (FIX:C).

C0371002 is a pivotal Phase 3 study designed to evaluate clinical efficacy and safety of PF-06838435 in adult male participants with moderately severe or severe hemophilia B (FIX:C ≤2% or ≤2 IU/deciliter [dL]) for the study duration of 6 years after a single administration of the study treatment. The study will enroll eligible participants who have completed at least 6 months of routine prophylaxis in the C0371004 study. The data for ABR_{total} from the Pre-Infusion Period will serve as historical control to test the Study C0371002 primary endpoint for non-inferiority. If non-inferiority of ABR_{total} with PF-06838435 treatment over routine prophylaxis is demonstrated, superiority will be tested on the ABR_{total}.

The guidance document by the Food and Drug Administration (FDA) were considered while developing this protocol.[2,3]

Overview of Hemophilia B

Hemophilia B, or Christmas disease, results from a deficiency of blood coagulation Factor IX (FIX). The gene for FIX is located on the X-chromosome and inherited in a classic x-linked pattern. Mutations may cause the gene to be ineffective leading to reduced FIX expression in males with a defective gene. Female carriers may have modest reductions in the FIX level.[4,5]

Factor IX, a serine protease, and factor VIII, a co-factor for FIX, work in concert to activate factor X, a central step in the coagulation cascade. The plasma factors are activated in the form of a cascade or "waterfall" (Macfarlane 1964; Davie and Ratnoff 1964) one after the other until the soluble plasma protein, fibrinogen, is transformed into a fibrinous clot. An effective clot cannot be formed without adequate levels of procoagulant factors. The level of coagulation factors in the plasma of normal individuals range from 50 to 150% (or 50-150 IU/dL) of the level in normal pooled plasma. Therefore, severity of the disease is determined by clinical features and factor coagulant activity.

Individuals with severe to moderately severe hemophilia B (circulating FIX level ≤2% or ≤2 IU/dL) frequently experience bleeding and recurrent spontaneous bleeding events into muscle, soft tissue, and joints (hemarthroses) starting from infancy and throughout adulthood. Examples of bleeding events include intracranial hemorrhage, deep muscle and joint hemorrhage, hematomas, retroperitoneal hemorrhage, bleeding following tooth extraction, post-surgical bleeding, easy bruising, and mucosal bleeding. Musculoskeletal hemorrhages can lead to recurrent hemarthroses and the development of target joints (a minimum of three bleeds into a single joint within a consecutive six-month period).[6] Such bleeding events inevitably result in progressive joint damage, leading to disabling arthritis with decreased physical and psychosocial quality of life (QoL) and socio-economic parameters. Intracranial hemorrhage is a leading cause of death among individuals with

hemophilia, with a mortality rate of up to 50% in adults as well as in children. Intracranial hemorrhage can occur after trauma, but as many as 50% of cases occur spontaneously.[7]

Development of inhibitory antibodies (ie, inhibitors) is the main complication of any factor replacement therapy, including FIX treatment.[8,9,10] Inhibitory antibodies develop in approximately 3-5% of patients with hemophilia B following exposure to factor replacement therapy. Hemophilia B inhibitors may present with anaphylactic responses to infusion of FIX products and in the presence of inhibitory antibodies, factor replacement is less effective. Therefore, acute management of bleeding requires agents that bypass FIX activity. Also, eradication of inhibitor through immune tolerance, typically implemented for long-term management of inhibitors in hemophilia A, is problematic and less effective in hemophilia B, especially in association with anaphylaxis. Thus, development of inhibitors significantly adds to the disease burden of hemophilia B patients.

Current Therapies for Hemophilia B

There is no available cure for hemophilia B. Treatment has focused on the replacement of FIX with intravenous (IV) administration of FIX concentrates to promote clotting. Current treatment is based on venipuncture and IV administration of either plasma-derived or recombinant FIX protein replacement therapy to raise the circulating FIX (FIX:C) activity level to the lowest effective level to achieve either resolution of bleeding (on-demand treatment) or prevention of bleeding (prophylaxis treatment).[4,11,12] The frequency of administration of FIX products varies and is tailored to the individual's clinical status, taking into consideration the type and frequency of bleed, and the goal of treatment. Both U.S. National Hemophilia Foundation and the World Federation of Hemophilia have established recommendations of plasma factor levels and duration of administration for different types of bleeds based on observational studies.[12,13] Improvements in FIX replacement therapy have vastly increased the QoL and life expectancy of individuals with hemophilia B.[4] Modified FIX agents with extended half-life provide more convenient dosing options and in some cases result in trough levels of FIX >12% of normal, a level that nearly eliminates spontaneous joint bleeds, can be maintained with weekly prophylactic dosing.[14,15,16,17,18]

Prophylaxis aims to convert a severe to a moderate phenotype through regular infusions of clotting factor. With full adherence in dosing regimen, prophylaxis is more effective than on-demand treatment for preserving joint health and has enabled affected individuals to participate more extensively in physical activity.[19,20,21,22] Utilization of prophylactic therapy for hemophilia has gradually increased among the adult population in the United States of America (USA), but is still not universally practiced. In the USA, as of 2014, an estimated 85% of children and 63% of adults with hemophilia were on prophylactic regimens.[23] Recent results from a multi-site study assessing adherence to prophylaxis and clinical outcomes in the Netherlands revealed only 43% of the patients adhered to the prophylactic regimen.[24]

Gene Transfer Therapy in Hemophilia

Gene transfer may manage hemophilia better and also remove the burden of frequent injections. Gene therapy for hemophilia works by packaging a corrected form of the FIX gene into a virus, most commonly an AAV. Using hepatotropic AAV serotypes allows the transgene to be delivered to hepatocytes in a highly efficient manner. Once delivered to hepatocytes, the gene is expressed and FIX enters to the circulation to contribute to the hemostatic process.

Hemophilia is an ideal candidate for gene transfer therapy because precise regulation of transgene expression of FIX is not required. The therapeutic range of FIX is remarkably wide, >1% to 150% of normal. Even attaining low level FIX activity between 1 and 5% of normal provides protection against chronic arthropathy and CNS bleeding. Patients with levels above 5% have much milder disease and only rarely experience spontaneous bleeding episodes, although they exhibit abnormal bleeding in response to hemostatic challenges such as surgery or trauma. Information about PF-06838435, including clinical experience, is provided in Section 2.2. Proof of concept of gene therapy was recently shown in a clinical study utilizing AAV8 gene transfer to patients with severe hemophilia B, sponsored by St. Jude Children's Research Hospital and University College London (SJ-UCL). In this study, levels of circulating FIX were achieved that effectively improved the phenotype of the patients with hemophilia B.

Spark Therapeutics has developed a customized AAV vector with enhanced liver tropism with which to deliver the highly active Padua variant of FIX. Using this approach in a Phase 1/2a trial of PF-06838435, Spark was able to achieve stable expression of FIX with all patients achieving mild status.[1]

2.1. Study Rationale

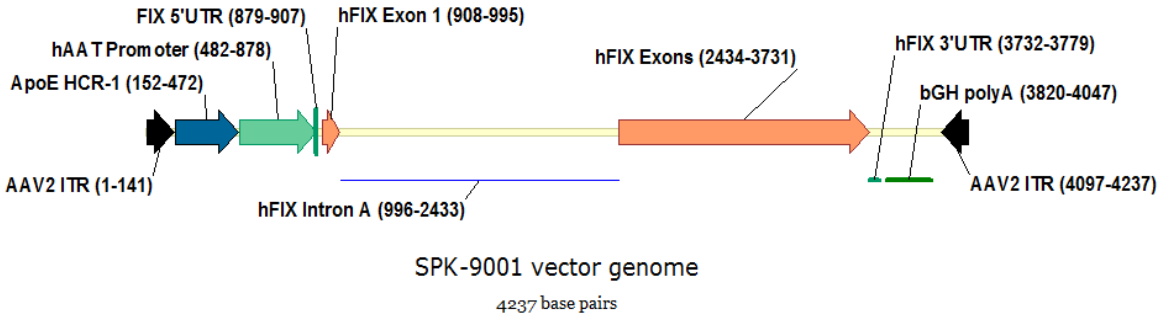
The published data from the Phase 1/2a study for PF-06838435 (SPK-9001-101) indicate that treatment of hemophilia B with PF-06838435 offers considerable clinical advantage over routine prophylactic treatment with FIX. A single infusion of PF-06838435 results in sustained FIX activity levels in the mild to normal range with associated low bleeding rates and a marked reduction in the number of infusions of FIX product (see Section 2.2.2).[1] This Phase 3 confirmatory study will compare efficacy of PF-06838435 treatment with routine prophylaxis with the objective to establish non-inferiority and possibly superiority.

2.2. Background

2.2.1. PF–06838435, Composition of the Vector

PF-06838435 is designed to require only a single administration into hemophilia B individuals, eliminating the disease burden associated with the condition and its treatment. It is a recombinant adeno-associated viral (rAAV) vector comprised of AAV-Spark100 (a bio-engineered hepatotropic AAV capsid) and hFIX39-Padua (a codon-optimized expression cassette encoding a naturally occurring FIX variant, FIX-Padua), under the regulatory control of the liver-specific modified hAAT promoter and portions of the apolipoprotein E hepatic locus control region [ApoE HCR-1] (Figure 2).

Figure 2. Schematic of PF-06838435 Vector Genome



A number of measures have been taken to improve both the performance and safety of the earlier AAV vectors; PF-06838435 differs from the earlier vectors in two main ways:

1. Capsid:

   - Utilizes a different AAV capsid, called AAV-Spark100. This a novel capsid engineered from a naturally-occurring AAV serotype, which shows a strong hepatotropic profile in mice and nonhuman primates (NHPs), comparable to AAV8; and

   - Increases resistance to circulating neutralizing antibodies (nAbs) to AAV in humans while maintaining good transduction efficiency in large animal models.

2. Cassette:

   - Encodes a naturally occurring FIX variant (ie, FIX-Padua), which has approximately 5-8 fold higher specific activity than wild-type FIX due to the substitution of an arginine for a leucine at amino acid position 338 (R338L).[25] Use of a FIX variant that has a higher specific activity than the wild-type protein may result in improved FIX:C activity levels.

2.2.2. Summary of Clinical Experience with PF–06838435

The Phase 1/2 Study (C0371005; formerly known as SPK-9001-101), in which 10 participants with FIX coagulant activity of ≤2% received a single infusion of PF-06838435 at 5×10^{11} vg/kg, reported no serious adverse events (SAEs), including no emergence of FIX inhibitors or thrombosis after a cumulative follow-up of 492 weeks. Asymptomatic increase in liver enzymes, suspected to be AAV capsid-specific immune response, was reported in two patients and resolved with short term prednisone treatment. Steady-state FIX coagulant activity was observed to be 33.7±18.5% (range, 14 to 81). After administration of PF-06838435, on cumulative follow-up of 492 weeks (range of follow-up in individual patients, 28 to 78 weeks), the mean ABR for treated bleeds was reduced from 11.1 events per year prior to administration (range, 0 to 48) to 0.4 events per year (range, 0 to 4) after administration (P = 0.02). Use of exogenous FIX was reduced as well (mean dose, 2908 IU/kg to [range, 0 to 8090] to 49.3 IU/kg [range, 0 to 376]; P = 0.004). A total of 8 of

10 participants did not use any factor and 9 of 10 did not have any bleeds after PF-06838435 administration.[1,26]

2.3. Benefit/Risk Assessment

The Phase 1/2 data has indicated that a single infusion of PF-06838435 would potentially allow patients to realize the benefit of FIX replacement without the need for frequent intravenous infusions, with an acceptable safety profile.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of PF-06838435 may be found in the PF-06838435 Investigator's Brochure, which is the single reference safety document (SRSD) for this study.[26]

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

Objectives	Endpoints
Primary	**Primary**
• To demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%).	Primary endpoint: • Non-inferiority on annualized bleeding rate (ABR) for total bleeds (treated and untreated) from Week 12 to Month 15 versus standard of care (SOC) FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion.
Secondary	**Secondary**
• Key secondary objectives: To demonstrate the efficacy of PF-06838435 in terms of the use of exogenous FIX, the treated bleeds, and FIX:C.	• Key secondary endpoints: o Non-inferiority on ABR for treated bleeds from Week 12 to Month 15 versus SOC FIX prophylaxis replacement regimen, comparing pre- and post-IP infusion. o Annualized infusion rate (AIR) of exogenous FIX from Week 12 to Month 15 versus AIR of FIX with SOC FIX replacement regimen pre-IP infusion. o Vector-derived FIX:C level at steady state (from Week 12 to 15 months) demonstrated to be greater than 5%. FIX:C will also be summarized descriptively by study visit.
• To compare additional efficacy parameters post-PF-06838435 infusion to baseline in order to further characterize PF-06838435 treatment, including use of exogenous FIX, information on bleeding events, and patient reported outcomes addressing health related quality of life, activities of daily living and general health status.	The following parameters will be compared with SOC FIX replacement regimen, comparing pre- and post-IP infusion from Week 12 to Month 15: • Annualized FIX consumption. • Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated. • Frequency of target joint bleeds. • Percentage of the participants without bleeds. The following parameters will be compared with SOC FIX replacement regimen, comparing pre- and post-IP infusion at 12 months:

Objectives	Endpoints

	• Change in joint health as measured by the Hemophilia Joint Health Score (HJHS) instrument.
	• PRO instruments:
	  • Haem-A-QoL Physical Health domain;
	  • HAL Complex Lower Extremity Activities Component Score.

• Safety and tolerability of PF-06838435, including immunogenicity, for the study duration of 6 years after PF-06838435 infusion	• Incidence and severity of adverse events collected during the study, as per details provided in Section 10.3.3.
	• Adverse Events of special interest:
	  • Hypersensitivity reactions;
	  • Clinical thrombotic events;
	  • FIX inhibitors,
	  • Hepatic malignancies.
	  • Drug related elevated hepatic transaminases that fail to improve or resolve
	  • Malignancy assessed as having reasonable possibility of being related to study drug
	• Other immunogenicity-based laboratory data including: neutralizing antibody (nAb) to AAV capsid, immune response (presumed T-cell activation) to AAV capsid protein and/or FIX transgene

• Assess durability of efficacy up to 6 years.	The following parameters will be assessed throughout the 6-year study period according to the SoA. Summaries will be provided for the overall follow-up period, as well as by yearly intervals: • Annualized Bleeding Rate for total bleeds (treated and untreated). • ABR for treated bleeds. • AIR of exogenous FIX. • Vector-derived FIX:C level by study visit and the geometric mean at each yearly interval. • Annualized FIX consumption. • Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated. • HJHS total score. • Frequency of target joint bleeds. • PROs instruments. • Haem-A-QoL Physical Health domain. • HAL Complex Lower Extremity Activities Component Score.

Objectives	Endpoints
Tertiary/Exploratory	**Tertiary/Exploratory**
• Pharmacodynamics of PF-06838435.	• Vector shedding of PF-06838435 as measured by PCR in plasma, saliva, PMBC, urine, and semen until 3 consecutive specimens test negative for the given specimen type. • FIX antigen levels.
• To compare joint health post-PF-06838435 infusion to baseline.	• Number of target joints. • Joint status as assessed by X-ray in some participants who consent to participate in an optional sub-study. • Joint status as assessed by MRI in some participants who consent to participate in an optional sub-study.
• Impact on coagulation.	• Coagulation activation tests: activated partial thromboplastin time (aPTT), INR, D-dimer, thrombin generation assay (TGA), and thrombin-antithrombin level (TAT). • Correlation of FIX activity between one stage assay and chromogenic straight assay.
• To compare additional efficacy parameters post-PF-06838435 infusion in order to further characterize PF-06838435 treatment in terms of patient-reported outcomes assessing hemophilia life impacts and global health status.	• PRO instruments: Haem-A-QoL (domains not previously specified), HAL (scores not previously specified), HLIQ, and EQ-5D-5L, in the first 12 months and annually in the follow-up period, years 2-6.

Estimands: The primary objective is addressed via the primary endpoint of ABR_{total}. Efficacy by ABR_{total} is summarized by the difference between pre- and post-treatment with PF-06838435; pre-treatment data will be obtained from the Pre-Infusion Period, including the lead-in Study C0371004. Steady-state FIX:C is a key secondary endpoint and the efficacy by FIX:C is summarized by the steady-state population mean post-treatment compared to a fixed threshold of 5%. Since no more than the single dose of study treatment on Day 1 will be administered during the study, there should be no treatment discontinuations. Resumption of FIX prophylaxis regimen is allowed as detailed in Section 6.5.1 and is assessed directly via secondary endpoints (AIR and FIX consumption). Data following resumption of FIX prophylaxis regimen will not be included in the analysis of ABR_{total}. There may be missing data from participants lost to follow-up, but it is anticipated to be rare. The primary endpoint, ABR_{total}, will utilize all applicable data to define the endpoints. Any missing data will not be imputed for the primary endpoint. The method to handle missing data of other endpoints will be discussed in the Statistical Analysis Plan (SAP). Baseline for change-from-baseline analyses will be defined based on the data collection method of each endpoint, but will reflect data before PF-06838435 (also referred to as IP) infusion.

4. STUDY DESIGN

4.1. Overall Design

This Phase 3, open-label, single-arm, multi-site study will compare the efficacy of a single intravenous (IV) infusion of PF-06838435 with routine FIX prophylaxis, in adult male

participants from the lead-in study (C0371004) with severe to moderately severe hemophilia B (≤2%). Eligible study participants will have completed a minimum 6 months of routine FIX prophylaxis therapy during the lead-in study (C0371004). The study duration for each participant in this study will be 312 weeks (see Section 1.3 for SoA). At least 50 participants will be screened to dose at least 40 participants with PF-06838435, and all 40 participants are expected to be evaluable.

4.2. Scientific Rationale for Study Design

Collecting prospective data in the Pre-Infusion Period and collecting data after PF-06838435 infusion allows for within-subject comparison analysis and a relatively low number of participants for a statistically robust study in hemophilia B, a rare disease. During the lead-in study, the eligible adult participants would have received prophylaxis with FIX replacement product as part of standard of care (SOC) along with on-demand infusions as necessary for bleeding events, for at least 6 months.

The planned study duration of 312 weeks for each participant takes into consideration the FDA Guidance for gene therapy[39] and includes 52 weeks of initial safety observation (Short-Term Monitoring Period) followed by 260 weeks of safety and durability follow-up (Long-Term Monitoring Period).

Based on non-clinical studies in NHPs, and the study NCT01687608 using hFIX-Padua and the Phase 1/2a study, it is not predicted that vector-derived FIX:C activity levels >150% of normal will be achieved in this study. However, thrombin-antithrombin levels (TAT) as thrombotic potential will be measured if vector-derived FIX:C activity levels >150% of normal are achieved in any participant during the study. Blood specimens for TAT during screening (prior to PF-06838435 infusion) will be used to establish baseline value. Also, global hemostasis markers will be measured at the end of Year 1.

Based on observation and experience from earlier clinical studies of liver-directed AAV gene transfer, including the SJ-UCL trial, additional earlier clinical studies, the Baxter trial (NCT#01687608), and the on-going Phase 1/2a study, participants may develop an apparent immune response to the vector capsid, as evidenced by a transient rise in transaminases (aspartate transaminase [AST] and/or alanine transaminase [ALT]) and an increase in AAV capsid-specific T cells in the peripheral blood. Immunomodulation will be instituted for these participants in an effort to limit the immunologic response in the liver and maintain endogenous FIX expression (Section 8.3.8).

4.3. Justification for Dose

The data from the Phase 1/2 study indicate that the single dose of 5×10^{11} vector genomes per kg (vg/kg) of body weight is safe and efficacious in patients with severe to moderately severe hemophilia B (≤2%) (see Section 2.2.2).[1]

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed the entire study including the End of Study (EOS) visit (Week 312).

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

5. STUDY POPULATION

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:

Type of Participant and Disease Characteristics

1. Participants must have completed at least 6 months of routine FIX prophylaxis therapy during the lead-in study (C0371004) prior to providing consent at the screening visit for this study.

2. Participants who have documented moderately severe to severe hemophilia B, defined as FIX:C ≤2%.

3. Participants must agree to suspend prophylaxis therapy for hemophilia B after administration of the IP. FIX replacement therapy is allowed as needed (see Section 6.5.1).

4. Acceptable screening laboratory values as follows:

   - Hemoglobin ≥11 g/dL;
   - Platelets ≥100,000 cells/µL;
   - Creatinine ≤2.0 mg/dL.

Sex

5. Male.

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

   Male participants are eligible to participate if they agree to the following for at least 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

6. 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.
   - For German sites please refer to Germany Appendix (Section 10.11.2.1).

5.2. Exclusion Criteria

Participants are excluded from the study (ie, not eligible) if any of the following criteria apply:

Medical Conditions

1. Anti-AAV-Spark100 neutralizing antibodies (nAb) titer ≥1:1 (ie, positive for nAb), performed by a central laboratory during screening.
2. Prior history of inhibitor to FIX or positive inhibitor testing as measured by the central laboratory ≥0.6 Bethesda Units (BU) during screening. Clinical signs or symptoms of decreased response to FIX.
3. Known hypersensitivity to FIX replacement product or intravenous immunoglobulin administration.
4. History of chronic infection or other chronic disease that investigator deems as an unacceptable risk.
5. Any concurrent clinically significant major disease or condition that the investigator deems unsuitable for participation 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.

~~6.~~ Alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) >2 × upper limit of normal (ULN), based on central laboratory results.

7. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN 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 FIX surgical prophylactic factor treatment in the next 15 months.

11. Participants using therapies that are restricted. See Section 6.5.2 for therapies not allowed during study participation.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

13. Active hepatitis B or C; HBsAg, HBV-DNA positivity, or HCV-RNA positivity.

14. Significant liver disease, as 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: FibroScan score >8 kPa units, Fibro Test/FibroSURE >0.48* or AST-to-Platelet Ratio Index (APRI) >1. In the investigator's opinion, if there is concern regarding the FibroTest results due to a confounding medical history (eg, proteinuria can impact FibroTest result), the investigator can perform a different assessment of liver fibrosis (eg, FibroScan or APRI) during the screening period.

*Please note: if a participant has a known history of Gilbert's syndrome, a FibroTest cannot be used for fibrosis testing. However, the participant could be tested using FibroScan or APRI.

15. Serological evidence of HIV-1 or HIV-2 infection with either CD4+ cell count ≤200 mm^3 or viral load >20 copies/mL.

Other Exclusions

16. 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 Germany Appendix (Section 10.11.2.2).

17. Unable to comply with scheduled visits, treatment plan, laboratory tests and other study procedures for up to six years post-infusion of PF-06838435 in the investigator's judgement.

    - For German sites please refer to Germany Appendix (Section 10.11.2.2).

18. Sensitivity to heparin or heparin induced thrombocytopenia.

19. 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.

    - For Japanese sites please refer to Japan appendix (Section 10.11.2.2).

5.3. Lifestyle Considerations

Participants are expected to remain compliant with inclusion criterion 5 at least until 3 consecutive ejaculate samples test negative for vector shedding (see Section 8.5.1).

One participant was noted to have increased LFTs in the setting of PPD in the long-term follow-up period. Upon discontinuation of PPD, his LFTs normalized but was later noted to have a decline in his steady-state FIX activity level. While this was a single episode and a definitive conclusion cannot be drawn, it supports monitoring of PPD during the study. Participants should be informed that PPD could contribute to abnormally elevated LFT results and thereby delay the infusion of the study drug. In addition, participants who report increased PPD (which is any amount of PPD greater than the baseline amount for that participant) at any time throughout the study, should have at a minimum local LFTs and FIX 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 serious adverse event (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.

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, or medical device(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-06838435
Type	Gene therapy
Dosage Form	Injectable
Strength	1.00×10^{13} vg/mL. This is the nominal strength. The actual strength for each lot will be provided for dosage calculation.
Dosage	5×10^{11} 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 cms (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 cms (6'2") tall individual.
Route of Administration	Intravenous infusion/injection.*
IMP and NIMP	IMP (investigational medicinal product).
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Study Intervention will be provided in a 2 mL vial. Each vial will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-06838435, SPK-9001, AAV-Spark100-hFIX39- Padua, Adeno-associated viral vector with human factor IX Padua gene.

* The Study Intervention/ IP will be administered using a prepared dosing solution (CCI [redacted] for Injection CCI [redacted]). The CCI [redacted] will be provided by the site (or infusion center). Further information is provided in the IP Manual.

For sites and Japan please refer to Section 10.11.1.3 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. Note that this bullet is also applicable to authorized staff at Infusion Centers.

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).

4. 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 Investigational Product (IP) Manual and it should be reviewed carefully. Once eligibility has been confirmed, the IP can be ordered noting that it will take approximately 3 weeks for product delivery. Prior to ordering IP, Sections 10.13.3 and 10.13.4 should be considered.

Wording in this paragraph is only required for study sites in France and is applicable to all sites participating in the study: No participants or third-party payers will be charged for investigational product.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open label using central randomization via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS)	This is an open label nonrandomized 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 prior to the start of study intervention administration for each participant. The infusion site will record the intervention assignment on the applicable case report form (CRF), 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, Sections 10.13.3 and 10.13.4 should be considered. For Japanese sites please refer to Japan appendix, Section 10.11.1.4.

Administration: If a participant does not receive a complete infusion for any reason, 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 nonprescription medications, including over-the-counter and alternative preparations such as herbal remedies, vitamins, and health food supplements) in the 30 days prior to screening and during screening must be recorded at Baseline on the participant's eCRF, according to instructions for eCRF completion. With the exception of FIX 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 10.13.4) during the Short-term Monitoring Period (up to and including 52 weeks post-infusion).
- The concomitant therapy associated with adverse events (AEs) reported during the Long-term Monitoring Period (Week 53 post-infusion to EOS). See Section 8.3.1 for AE recording requirements.
- All surgical procedures, including elective surgeries, will be recorded throughout the study. Additional information regarding surgeries (eg, blood loss and/or transfusion amounts) will be collected on relevant CRF(s).

The records 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 routinely for a pre-existing condition should be on a regimen, which has been stable for at least 3 weeks, and ideally dosage should not be changed during the first year after PF-06838435 infusion.

6.5.1. Allowed Therapy

During the study participants are requested to suspend their FIX prophylaxis regimen after infusion of PF-06838435, but may take:

- FIX 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 FIX to treat the bleed because the dose of factor concentrate should include the recent steady-state PF-06838435 induced FIX activity levels to avoid overdosing resulting in a potential thrombotic event. The table in Appendix 8 provides guidelines for target FIX levels based on bleed type.
- A participant may resume prophylaxis if the PF-06838435 treatment is not efficacious, defined for this study as:
  - FIX activity after 12 weeks of ≤2% (in the absence of a confirmed FIX 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 FIX 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 discuss the case with the sponsor's medical monitor prior to resumption of prophylaxis. Dosing of prophylaxis will take into account the current steady-state FIX activity level. A participant who resumes prophylaxis may choose to discontinue it; however, prior to discontinuation, the investigator is to discuss with the sponsor's medical monitor.

Additional allowed therapies include the following:

- COX-2 inhibitors and topical NSAIDs, where medically necessary
- HIV therapy

6.5.2. Disallowed Therapy

The following concomitant medications are not permitted during the study:

- Blood products such as red blood cells (RBC), 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), anticoagulants (eg, warfarin, apixaban), regular long-term use of NSAIDs (eg, ibuprofen, naproxen). However, low dose aspirin (<100 mg/day) and PRN/short-term use of NSAIDs may be used where medically necessary. Please contact the sponsor's medical monitor if there are any questions regarding the use of medications that may prolong bleeding.
- Concomitant use of another investigational therapy; concurrent participation in another interventional clinical study is not allowed.
- Bypassing agents (eg, factor VIIA/ rFVIIA, activated prothrombin complex concentrate), except in situations where it is medically necessitated (ie, medical emergencies).

For COVID-19 vaccinations please refer to Section 10.13.4.

6.6. Dose Modification

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

The dose of 5×10^{11} vector genomes/kg body weight will be modified for a participant with BMI >30 kg/m^2 (See the table in Section 6.1).

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

Since no more than the single infusion of PF-06838435 on Day 1 will be administered during the study, this section is not applicable. See Section 6.4 for 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 own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- At the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

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

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

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 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 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 will be considered lost to follow-up.

- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

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, where indicated in the SoA, 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 post-infusion of PF-06838435 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-06838435.

Screening Period

Screening procedures will be conducted according to the SoA (Section 1.3). The Screening Period will end and Baseline Period will commence when a participant is determined to be eligible for the study.

Baseline Period and Scheduling the PF-06838435 Infusion

Baseline procedures will be conducted according to the SoA (Section 1.3). PF-06838435 is to be ordered at the beginning of the Baseline Period after confirming eligibility. Prior to ordering IP, Sections 10.13.3 and 10.13.4 should be considered. The IP will require approximately 3 weeks for shipment. Also, the timing of the participant's next FIX prophylaxis dose is to be planned to occur on the same day of PF-06838435 infusion (Day 1).

The Screening and Baseline period may be extended, upon consultation with the sponsor's medical monitor. 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) will be conducted 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 (Section 1.3).

Blood for LFTs are to be drawn and tested locally and centrally prior to dosing participants (up to 3 days prior to Day 1/ Visit 3 is acceptable). Utilize mobile phlebotomy/ home health services as needed, and if possible. Local LFTs are required to be reviewed 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. These LFT results should be entered into the CRF as an unplanned visit.

Note: Participants should be informed that 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 5.1and 5.2) to receive PF-06838435 infusion. Prior to dosing, Sections 10.13.3 and 10.13.4 should be considered. The IP should NOT be thawed and prepared without this eligibility confirmation AND affirming that the participant is physically present at the clinic (or infusion center).

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

If the infusion of PF-06838435 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 towards efficacy assessment.

For Japanese sites please refer to Japan appendix, Section 10.11.1.4.

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 prior to Week 312, the early discontinuation visit will follow the same procedures as the Week 312 visit (End of Study), per 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. 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 post-infusion 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 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 deviations.

- ECG
- Liver ultrasound
- HJHS
- Global Hemostasis Markers

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 FIX replacement (including date, time, reason, and dose) required to treat the bleeds in the eDiary (see Appendix 7). If bleeding episodes or treatments are not entered in the eDiary during the appropriate time window, 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. The bleeding episodes and exogenous FIX replacement data mentioned above will be referred to as "eDiary data" regardless of how it is collected (ie, via the handheld device or according to the process in place).

As part of the process in place, participants should communicate all bleeds and all relevant infusion data that was not entered into the eDiary within the appropriate time window (ie, "late eDiary entries") to the investigator (or appropriate site staff member). 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). In the event of continued late eDiary entries or non-use of the eDiary device (ie, non-compliances), the site staff should remind the participant that he will be expected to report all bleeds and all relevant infusion data to the site staff on a contemporaneous basis and that he may be expected to surrender his eDiary. The site staff will be expected to enter the information, provided by the participant, into the CRFs with appropriate source documentation in the participant's medical record for the remainder of the study.

In the event that a participant may have to resume FIX prophylaxis treatment at some point after IP infusion, prophylaxis FIX infusion data will not have to be reported on the eDiary (or conveyed to the study site staff on contemporaneous basis) after Week 78 (Visit 14). However, bleeds and non-prophylactic infusions (eg, On-demand and Preventative) would continue to be reported for these participants throughout the course of the study. Prescribed FIX prophylaxis replacement therapy will continue to be captured (eg, particularly any change in regimen), by the site staff, using the "FIX Replacement (Prescribed Dose)" CRF.

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

Bleeding episodes requiring treatment with FIX product 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.

8.1.2. Joint Assessments

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

8.1.2.1. Hemophilia Joint Health Score (HJHS)

Swelling, on motion Joint assessments will be performed using the Hemophilia Joint Health Score (HJHS) version 2.1 (Appendix 12) 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.

8.1.2.2. Magnetic Resonance Imaging (MRI) to Evaluate Joints

Some participants (n~20), who consent to participate in an optional sub-study, will undergo MRI exams to assess damage within joints by evaluating soft-tissue changes and osteochondral changes. These participants will be chosen based on the availability of MRI at the site and participant willingness to undergo the procedure. The MRI scanning protocol will include acquisition of knees, elbows, and ankles. MRI scans will be acquired according to the SoA. If the MRI can't be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4/ Visit 6. If the baseline MRI 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 3 (Visit 17) and 6 (Visit 20) year follow-up MRIs. All details of the MRI acquisition will be captured in a separate scanning guide. At a minimum, joint images will be reviewed following the extended MRI scale with a final score combining soft-tissue and osteochondral sub-scores. All details of the independent review will be captured in a separate Imaging Charter.

8.1.2.2.1. 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.

MRI images will be reviewed by a central review facility. The purpose of this review is to evaluate images for soft tissue and osteochondral changes. 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 as per site protocols.

MRI images will not be evaluated using a real-time reading paradigm and therefore there may be a significant delay between image submission and realization of an incidental finding.

8.1.2.3. X–ray Assessments to Evaluate Joints

Some participants (n~40), who consent to participate in an optional sub-study, will undergo X-ray assessment of knees, elbows, and ankles to assess damage within joints as detectable at a radiologic level. For German sites please refer to Germany Appendix (Section 10.11.2.5). X-rays will be acquired according to the SoA. If the X-ray can't be performed during the baseline 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 3 (Visit 17) and 6 year (Visit 20) follow-up X-rays. 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.[27] All details of the independent review will be captured in a separate Imaging Charter.

8.1.3. Patient–Reported Outcomes (PROs)

Patient-reported outcomes (PROs) implemented in this study are the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), the Hemophilia Activities List (HAL), the Hemophilia Life Impacts Questionnaire (HLIQ), and the EQ-5D-5L Additionally, the Patient Global Impression of Change (PGIC-H), a single item assessment of the participant's overall impression of change in their life with hemophilia since being enrolled in the study and infused with PF-06838435 will also be administered.

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

They should be completed as per the SoA during the scheduled site visits, especially the baseline visit, using a tablet device that will be provided to each site. Baseline PRO assessments need to be done prior to start of infusion if not done at baseline visit. If the post-infusion PROs can't be performed at a particular visit, they should be performed at the next 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.

8.1.3.1. Haemophilia Quality of Life Questionnaire for Adults (Haem–A–QoL)

The Haem-A-QoL is a disease specific measure of health-related quality of life in 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); Feelings (4); View of Self (5); Sport/Leisure (5); Work/school (4); Dealing with Haemophilia (3); Treatment (8); Future (5); Family Planning (4); and Partnership and Sexuality (3). Scores are calculated by domain and a single total score. Physical health domain is considered as the primary domain in this questionnaire and will be further assessed using the anchor-based method for each yearly visit. See Section 10.9.1 for the instrument.

8.1.3.2. Hemophilia Activities List (HAL, Version 2)

The Hemophilia Activities List (version 2) is a multiple domain measure of the impact of hemophilia on functional abilities in adults. The 7 domains of this instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8); Lower (leg) functioning (9); Upper (arm) functioning (4); Transportation (3); Self-care (5); Household tasks (6); and Sports/Leisure (7). 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. The component score of "complex lower extremity activities" is considered the most important in this questionnaire and will be assessed using the anchor-based method for each yearly visit. See Section 10.9.2 for the instrument.

8.1.3.3. Patient Global Impression of Change – Hemophilia (PGIC–H)

The Patient Global Impression of Change – Hemophilia (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 and infused with PF-06838435. The recall period for the PGIC-H is "since the start of the study". The response scale is a 7-point categorical response scale centered around 'no change' with 3 grades of improvement and 3 grades of worsening. See Section 10.9.3 to view the item.

8.1.3.4. Hemophilia Life Impacts Questionnaire (HLIQ)

The Hemophilia Life Impacts Questionnaire (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 (VRS) scored from 0 to 4, while 4 items are gated such that responding 'yes' branches to a 5-point, ordinal VRS 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 (VRS) scored from 0 to 3. Higher scores on the VRSs indicate greater impact due to living with or treating hemophilia. See Section 10.9.4 for the HLIQ instrument.

8.1.3.5. EQ–5D–5L

Developed by the EuroQoL Group, the EQ-5D-5L (EuroQol, 5 dimensions, 5 levels) is considered the premier measure of health status used in the assessment of the Quality Adjusted Life Year (QALY). 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 (VAS) anchored by worst and best imaginable health on a 0 to 100 scale where participants are asked to indicate where on the scale they rate their current health. See Section 10.9.5 for the instrument.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- Only complete physical examinations will be conducted during this trial. A complete physical examination will include, at minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (required at screening) 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.

    - *Note: 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. Electrocardiograms

- 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, QT, and corrected QT intervals (QTc).

8.2.4. 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 Time Period and Frequency for Collecting AE and SAE Information).

8.2.5. Liver Ultrasound

All participants will undergo ultrasound imaging of the liver at times specified in the SoA. Details of the ultrasound acquisition will be provided in a separate scanning guide. Ultrasound images will be acquired locally by an appropriately trained individual.

8.3. Adverse Events and Serious Adverse Events

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

The definition of adverse events of special interest can also be found in Section 8.3.9.

AE 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 that caused the participant to discontinue the study (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 Demographics, 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 investigational product), through and including 6 years after the last administration of the investigational product, or at EOS for participants who discontinue. The active collecting period for this study is categorized into Short-Term and Long-Term Monitoring Period as 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 event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

During the Short-Term Monitoring Period (up to and including 52 weeks post-infusion) all SAEs (including medically important events, see Appendix 3) and AEs will be collected.

During the Long-Term Monitoring Period (Week 53 post-infusion to EOS) the following AEs will be collected:

- SAEs (including medically important events, Appendix 3).
- Non-serious AEs determined to be related to IP by the investigator or where causality is unknown.

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

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form immediately 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 Non-serious 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 directly observed and spontaneously reported AEs and SAEs during the Short-Term and Long-Term Monitoring Periods per details provided in Section 10.3.3.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (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.

- **Wording in this paragraph is applicable to study sites in France only:** Pursuant to a sponsor's safety reporting obligations under 21 Code of Federal Regulations (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 Section 8.3.4 of the protocol.

- For Japanese sites please refer to Japan appendix, Section 10.11.1.4.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product 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

An exposure during pregnancy (EDP) occurs if:

- A male participant who received study intervention exposes a female partner prior to or around the time of conception.

- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:

- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by the vascular system.

- A male family member or healthcare provider who has been exposed to the study intervention by the vascular system then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant's partner, 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. Details of the pregnancy will be collected after the start of study intervention and until the end of study participation.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the 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.

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).

Abnormal pregnancy outcomes are considered SAEs. 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 including 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 study intervention.

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.

8.3.5.2. Exposure During Breastfeeding

Not applicable.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. 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. Immunogenicity

8.3.6.1. Analysis of Anti– PF–06838435 Antibodies and Neutralizing Anti PF–06838435 Antibodies

Whole blood specimens of approximately 4-5 mL to provide a minimum of 2 mL of serum will be collected for determination of anti-AAV capsid protein antibodies (ADA) and approximately 4 mL of whole blood will be collected to provide a minimum of 2 mL of serum for determination of neutralizing antibodies (Nab) to PF-06838435 (specifically to the SPK-100 AAV capsid) as specified in the SoA (Section 1.3) of the protocol. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for determination of anti-PF-06838435 antibodies and neutralizing anti-PF-06838435 antibodies may also be used for additional characterization of the immune response and/or evaluation of the bioanalytical method, or for other internal exploratory purposes. These data will be used for internal exploratory purposes. The neutralizing anti-PF-06838435 antibodies may be stored at 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.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. Samples determined to be positive for ADA may be further characterized for NAb.

The immunogenicity samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the immunogenicity 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.

8.3.6.1.1. Immunology Exploratory (PBMC and binding IgG vs IgM antibody response)

The exploratory immunology samples (peripheral blood mononuclear cells [PBMC] and serum for IgG and IgM antibody response) are being collected to characterize the cell and humoral immune response to the vector capsid protein.

These samples will be destroyed upon or before completion of the last clinical study report for the study.

8.3.6.2. Analysis of FIX Inhibitor

During all study periods, blood samples will be collected for measurement of FIX inhibitor as specified in the SoA section of the protocol.

- Samples collected will be analyzed using a validated analytical method in compliance with standard operating procedures (SOPs). 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 central laboratory may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation. These data will not be included in the clinical study report (CSR).

8.3.6.3. Analysis of Cellular Immune Response by ELISPOT (enzyme–linked immuno–spot)

This is a quantitative method for measuring relevant parameters of T cell activation. The sensitivity of ELISPOT allows the detection of low-frequency antigen-specific T cells that secrete cytokines and effector molecules. Specimen for PBMC by ELISPOT will be collected at times specified in the SoA.

Specimen is to be collected prior to initiating the corticosteroid treatment. If not collected prior to initiation, it must be collected within 24 hours of administering corticosteroids. 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, ranitidine) for the duration of the corticosteroid course.

Whole blood specimens (approximately 48 mL) will be collected in sodium heparin vacutainer tubes to provide PBMC to monitor T cell responses to AAV capsid and transgene products at times specified in the SoA of the protocol.

Detailed collection, processing, storage, and shipment instructions are provided in the central laboratory manual.

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.

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

The disease related events (DREs) for this study include episodes of bleeding related to hemophilia B. 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 S/AE.

Bleeding, not due to the participant's hemophilia, will be recorded as an AE, and not a DRE. 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. Immunomodulation Optimization (Presumed T-Cell Activation)

A tapering course of oral corticosteroids (ie, 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, but viruses may be causal. It is also possible that an elevation in liver transaminases is not due to immune responses.

While not all elevations in liver transaminases may be immunologically mediated, the decision to treat will not be delayed while attempting to decipher the etiology. 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, ranitidine) for the duration of the corticosteroid course. Due to the importance of timely intervention of corticosteroids, decisions to begin treatment will be based on local laboratory values. Based on guidelines published by the American Association for the Study of Liver Diseases and in the absence of alternative etiology, and from the study data of the SJ-UCL group along with the Phase 1/2a study, treatment with corticosteroids for vector-induced hepatitis would be highly recommended if any of the criteria are met:

- Transaminase increase, per local lab results:
    - Single increase ≥1.5 fold of the lowest transaminase value, since screening into the study and prior to infusion.
        - For example, a participant may have an ALT of 35 U/L prior to infusion, but at week 5 the value increases to 53 U/L. This increase would be enough to initiate treatment even though the values are within normal range.
    - Consecutive increases (an increase in transaminases on two subsequent blood tests independent of FIX:C values). Following the trend is especially important as it is possible that LFTs seen post-infusion may be below that seen during screening/baseline. In these situations, following for consecutive increases/ trends is particularly important.
        - For example, a participant may have an ALT of 18 U/L. Then on the next two lab draws (obtained during a study visit or unplanned visit) the values increase to 22 U/L and then 26 U/L, this increase would be enough to initiate treatment even though the values are within normal range.
        - For example, a participant may have an ALT of 38 U/L as the baseline value. Post-infusion, the ALT values are lower than that seen during screening and range from 18-22 U/L over the first few weeks. Then on the next 2 laboratory draws (obtained during a study visit or unplanned visit), the values increase to 29 U/L and then 37 U/L. This increase would be enough to initiate treatment even though the values are both below baseline and within normal range.
    - **Note:** Any delay or deviation in the initiation of corticosteroid treatment, based on the transaminase increase points above, must be discussed with the sponsor's

medical monitor in the context of the overall clinical management plan to ensure participant safety.

- FIX:C decrease, per local lab results:
  - Single significant decrease, not associated with a recent infusion of external FIX product.
    - For example, a participant may have a FIX:C of 51 IU/mL at Week 4, but at Week 5 the value decreases to 28 IU/mL. This decrease would be enough to initiate treatment.
  - Consecutive decreases (a decline in FIX activity on two consecutive blood tests independent of transaminase values) if occurring during the first 120 days post-infusion.
    - For example, a participant may have a FIX:C value of 34 IU/mL at Week 4. Then on the next two lab draws (obtained during a study visit or unplanned visit) the values decrease to 27 IU/mL and then 24 IU/mL, this decrease would be enough to initiate treatment.

    If occurring beyond 120 days post-infusion, the investigator should contact the sponsor's medical monitor to discuss prior to initiating corticosteroids unless otherwise clinically indicated (eg, a decline in FIX:C level thought to be beyond the margin of error for FIX:C assay or biological fluctuation).

  - **Note:** Any delay or deviation in the initiation of corticosteroid treatment, based on the FIX:C decrease points above, must be discussed with the sponsor's medical monitor in the context of the overall clinical management plan to ensure participant safety.

Table 1. Recommended Regimen for Oral Corticosteroids

Schedule (oral corticosteroid treatment regimen)	Prednisolone/Prednisone (mg/day)
Week 1	~60 – 100*
Week 2	60**
Week 3	40
Week 4	30
Week 5	30
Week 6	20***
Week 7	15
Week 8	10

* Mainly based on body weight.
** See the paragraph below this table.
*** 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. If available, ELISPOT results will be monitored during tapering.

Approximately 60-100 mg/PO (orally) qd (once a day) of oral corticosteroids for the first week is recommended as the starting dose unless the investigator believes a different regimen should be implemented based on the participant's medical history. Per the judgment of the investigator, the first week dose can be extended to another week if the participant has no adverse effect. The subsequent prednisolone/prednisone taper should not be started until the ALT and/or AST have declined at least two consecutive lab draws, or have returned to approximately baseline (pre-administration) levels and any decline in FIX:C activity has plateaued. See Table 1 above.

The following schedule of combined oral corticosteroids and intravenous corticosteroids (methylprednisolone) is recommended if there is no evidence of resolution of transaminase elevation while on oral corticosteroids treatment alone.

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 since the exact regimen and course will depend on clinical circumstances. 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 FIX:C 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 adverse events connected to their use.

- If 2 or more participants are non-responsive to immunomodulatory regimens, or if the value of the transaminases continues to rise, consideration of more intensive immunomodulatory regimens will be entertained per discussion between the sponsor

medical monitor and the investigator. The sponsor will convey the information to the External Data Monitoring Committee (eDMC).

8.3.9. Adverse Events of Special Interest

All AESIs must be reported as an AE or SAE following procedures described in Section 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 events assessed as non-serious AEs.

8.3.9.1. Lack of Efficacy

Not applicable

8.3.10. Thrombotic Potential Assessments (ONLY for participants who reach vector-derived FIX:C Activity Levels >150% After the Infusion of PF–06838435)

Based on non-clinical studies in NHPs, the prior Baxter study using hFIX-Padua, and the Phase 1/2a study, it is not predicted that vector-derived FIX:C activity levels >150% of normal will be achieved in this study. However, thrombin-antithrombin levels (TAT) as thrombotic potential will be measured if vector-derived FIX:C activity levels >150% of normal are achieved in any participant during the study. Blood samples for TAT obtained during screening will be used to establish baseline value. Additional testing can be performed upon discussion with the medical monitor including by not limited to D-dimer, TGA, and/or prothrombin fragments 1+2.

8.3.11. Medication Errors

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

Exposures to the investigational product 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 investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participant;

- Not performing a flush of the IV line at the conclusion of the IP 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 non-serious, 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-06838435 greater than 5×10^{11} vg/kg of the 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:

- Contact the sponsor's medical monitor within 24 hours.

- Closely monitor the participant for any AE/SAE and laboratory abnormalities.

- Document the quantity of the excess dose as well as the duration of the overdose in the Medication Error CRF.

- Overdose is reportable to Safety **only when associated with a SAE**.

8.5. Pharmacokinetics

All samples collected from participants for plasma factor IX activity levels as per the SoA will be analyzed at a certified clinical laboratory by two different one stage assays along with analysis by chromogenic assay. Results will be used to determine vector-derived FIX:C activity level at steady-state (Week 12 and after).

Measurement of the vector-derived FIX: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 FIX:C activity levels will take into consideration data entered in the eDiary. As FIX inhibitors or T-cell

mediated immune response may impact the FIX activity levels, this information will also be taken into account while deriving FIX:C activity levels.

- During all study periods, blood samples will be collected for measurement of vector-derived FIX:C as specified in the SoA section of the protocol.

- Samples collected will be analyzed using a validated analytical method in compliance with standard operating procedures (SOPs). 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. Any deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation. These data will not be included in the CSR.

8.5.1. Samples for Vector Shedding Assays

Samples of plasma, saliva, PBMC, urine, and semen will be collected as specified in the SoA for analysis of vector shedding.

In the event that a participant is unable to provide any semen for vector shedding over the course of 1 month post-IP infusion, future attempts to provide semen samples can be stopped provided that the participant provides 3 consecutive negative PBMC samples before no longer being required to follow the restrictions within inclusion criteria #5 in Section 5.1.

Some participants (n = 12), who consent to participate in an optional sub-study, are expected to provide additional (2 hours ±30 minutes, 24 hours ±3 hours, 72 hours ±4 hours after completion of IP infusion and IV line flush on Day 1) samples (plasma, PBMC, saliva, semen, and urine).

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.

8.6. Pharmacodynamics

Pharmacodynamic markers such as thrombin generation assay (TGA) will be measured for all participants. Global hemostasis markers will also be collected (Appendix 2).

The samples will be collected as per the SoA and detailed in the Laboratory Manual.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD 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. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

As part of understanding the PD of the investigational product, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes. These data will not be included in the CSR.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs. These data will be used for internal exploratory purposes and will not be included in the CSR.

8.6.1. Samples for FIX Antigen Levels

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

8.6.2. Samples for Thrombin Generation

During all study periods, blood samples (3.5 mL) to provide approximately 600 µL plasma for TGA analysis will be collected into appropriately labeled tubes containing sodium citrate at times specified in the SoA.

Details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the central lab manual.

8.6.3. Samples for D-dimer

Blood samples will be collected per the SoA and as specified in the Laboratory Manual to measure D-dimer.

8.6.4. Shipment of Pharmacodynamic Samples

The shipment address and analytical laboratory contact information will be provided to the investigator site prior to initiation of the study.

8.7. Genetics

8.7.1. Specified Genetics

A blood sample for DNA isolation will be collected as specified in the Laboratory Manual, only if a participant has not undergone FIX genetic testing in the past or the results of such testing are not available it the source documents. DNA samples will be analyzed for the purpose of determining the underlying FIX gene mutation.

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 Biospecimen collection is not required for this study.

8.8. Biomarkers

Not applicable.

8.9. Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. Estimands and Statistical Hypotheses

The details of statistical methodology will be specified in the Statistical Analysis Plan (SAP).

The hypothesis testing of the primary endpoint is listed below.

- To demonstrate non-inferiority (NI) of PF-06838435 to routine prophylaxis on difference in ABR_{total} (NI margin of 3 bleeds/year) by comparison of post-infusion of PF-06838435 ABR_{total} from Week 12 to Month 15 versus pre-IP infusion ABR_{total} collected during Pre-Infusion Period, in participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%), who have tested negative for nAb and have no medical history of FIX inhibitor. The primary objective for ABR_{total} will be considered to have been met if non-inferiority is demonstrated. Additionally, if non-inferiority is demonstrated on ABR_{total}, subsequent testing for superiority will be conducted on the endpoint. Superiority of ABR_{total} is considered a secondary analysis.

9.1.1. Estimands

The primary objective is addressed via the primary endpoint of ABR_{total}. Efficacy by ABR_{total} is summarized by the difference between pre- and post-treatment with PF-06838435; pre-treatment data will be obtained from the Pre-Infusion Period, including the lead-in Study C0371004. Steady-state FIX:C is a key secondary endpoint and the efficacy by FIX:C is summarized by the steady-state population mean post-treatment compared to a fixed threshold of 5%. Since no more than the single dose of study treatment on Day 1 will be administered during the study, there should be no treatment discontinuations. Resumption of FIX prophylaxis regimen is allowed as detailed in Section 6.5.1 and is assessed directly via secondary endpoints (AIR and FIX consumption). Data following resumption of FIX prophylaxis regimen will be excluded from the analysis of ABR_{total}. There may be missing data from participants lost to follow-up, but it is anticipated to be rare. The primary endpoint, ABR_{total} will utilize all applicable data to define the endpoints. A description of the data which are not applicable for ABR_{total} (eg, data following the resumption of prior prophylaxis therapy) will be discussed in detail in the Statistical Analysis Plan (SAP). Any missing data will not be imputed for the primary endpoint. The method to handle missing data of other endpoints will be discussed in SAP. Baseline for change from baseline analyses will be defined based on the data collection method of each endpoint, but will reflect data before IP infusion.

9.2. Sample Size Determination

Participants who complete the lead-in protocol C0371004 will be screened to achieve desired sample size of 40 participants, and eligible participants will be assigned to study intervention. All 40 participants are expected to be evaluable in this one-armed study.

When all 40 participants have completed at least 15 months of follow-up post-infusion of PF-06838435, the ABR_{total} data will provide at least 90% power (one-sided test with α=0.025) to demonstrate non-inferiority of gene therapy compared to prophylaxis treatment on the difference in ABR_{total}, using a repeated measure negative binomial regression, with a non-inferiority margin of 3.0 bleeds/year. The assumed background rate of annualized bleeding is a conservative 5.0 and the assumed annualized bleeding rate post-PF-06838435 is 1.5. The details of non-inferiority margin selection are included in Appendix 10.

The number of participants may exceed 40, because all participants who complete the lead-in study (C0371004) and meet other eligibility criteria will be allowed to participate in this study.

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[1]	All participants enrolled in the study and received IP.
Safety	All participants enrolled in the study and received IP, which is the same as dosed population.
Intent To Treat (ITT)	ITT population is not defined for this study since it is not a randomized study.
Evaluable	All participants are enrolled in the study and take study medication and no significant interruption of efficacy measurement.[2]

1. Dosed population is the primary analysis population for efficacy endpoint analysis, while evaluable population is the analysis population for sensitivity analysis.
2. Significant interruption will be assessed after discussion between the investigator and the medical monitor, eg, if a participant requires a major surgery, this will be a significant interruption of measurement.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, any multiple testing procedures (to control the overall type I error of primary, secondary hypothesis test), and procedures for accounting for missing, unused, and spurious data. The overall probability of Type 1 error alpha for primary statistical tests, and other tests included in the multiple testing procedure, is controlled at .05 (or one-sided .025). 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 focused on 15 months follow-up after infusion of PF-06838435, with endpoints in below table. The planned endpoints after the primary analysis, so called final analysis, are focused on extended efficacy and longer-term safety.

Since there is only one primary endpoint, no multiplicity correction is needed. A gatekeeping process will be applied to control multiplicity of testing multiple secondary endpoints. The subsequent hypothesis testing will only be applied after success on a previous hypothesis test. The analyses cease when a failure occurs. The sequence of the gatekeeping process will be further detailed in SAP.

Endpoint	Primary analysis Statistical Analysis Methods
Primary	• ABR for total bleeds (treated and untreated bleeds from Week 12 to Month 15) will be compared to pre-infusion of PF-06838435 (under SOC FIX prophylaxis replacement regimen). A repeated measure negative binomial regression model will be used to do the hypothesis test on non-inferiority with one-sided test with the specified α. If the non-inferiority on ABR_{total} is established, subsequently testing for superiority will be conducted.
Secondary	• ABR for treated bleeds from Week 12 to Month 15 will be compared to pre-infusion of PF-06838435 (under SOC FIX prophylaxis replacement regimen) using a repeated measure negative binomial regression, with a non-inferiority margin of 3.0 bleeds/year. • AIR for FIX from Week 12 to Month 15 versus AIR during SOC FIX replacement regimen will be tested for superiority. Paired T-test will be used to do this hypothesis testing. • Vector-derived steady state FIX:C (Week 12 to Month 15) will be compared to a threshold of 5% using a one-sided, one sample T-test. FIX:C will be descriptively summarized by study visit. • FIX consumption, from Week 12 to Month 15, similar method as applied to AIR will be used to do hypothesis testing on this endpoint. • Number of bleeding events of specific type from Week 12 to Month 15: spontaneous and traumatic, and untreated. Similar method applied to ABR_{total} will be used to test these endpoints. • Frequency of target joint bleeds from Week 12 to Month 15 will be summarized. The number of target joints bleeds will be compared to baseline. Similar method applied to ABR_{total} will be used to test these endpoints. • Percentage of participants without bleeds (total bleeds and treated bleeds) will be summarized by type from Week 12 to Month 15. • HJHS for first 12 months post-infusion of PF-06838435 will be compared to baseline using 2-sided paired T-test. • PRO endpoints (Haem-A-QoL Physical Health domain, HAL Complex Lower Extremity Activities Component Score) 12 months post-infusion of PF-06838435

Endpoint	Primary analysis Statistical Analysis Methods
	will be summarized and compared to baseline to assess the improvement from baseline if baseline is available.
Exploratory	• Will be described in the statistical analysis plan.
	Final analysis
Secondary	• Annualized Bleeding Rate for total bleeds (treated and untreated bleeds from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up) will be analyzed. • Vector-derived steady state FIX:C (from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up) will be analyzed. FIX:C will be descriptively summarized by study visit. • Annualized FIX Infusion Rate (on-demand and Prophylaxis, AIR from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up) will be tested for superiority by comparing pre- and post-infusion of PF-06838435. • Annualized Bleeding Rate for treated bleeds (from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up) will be analyzed. • FIX consumption from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up. • Number of bleeding events of specific type from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up: spontaneous and traumatic, and untreated. • HJHS yearly after first 12 months and 6 years of follow-up will be compared to baseline to assess the improvement from baseline. • Frequency of target joint bleeds from Month 15 to Month 24, by yearly intervals after 24 months, and across 6 years of follow-up will be summarized. The number of target joints bleeds will be compared to baseline. • PRO endpoints (Haem-A-QoL Physical Health domain, HAL Complex Lower Extremity Activities Component Score) yearly after first 12 months and 6 years of follow-up will be compared to baseline to assess the improvement from baseline.
Exploratory	• Will be described in the statistical analysis plan.
	MRI Sub-Study
Exploratory	• Joint images will be reviewed following the extended MRI scale with a final score combining soft-tissue and osteochondral sub-scores, and compared to baseline (at year 3 and after 6 years of follow-up).
	Vector Shedding Sub-Study
Exploratory	• A subset of participants (N=12) will have more extensive vector shedding analysis performed in an effort to further characterize the kinetics of vector shedding.

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 statistical analysis plan finalized before database lock.

9.4.3. Other Analyses

FIX:C antigens, pharmacodynamic, and biomarker exploratory analyses will be described in the SAP.

9.5. Interim Analyses

There is currently no plan for a formal interim analysis. As this study is a single arm open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

9.5.1. External Data Monitoring Committee (eDMC)

This study will use an external data monitoring committee (eDMC). The eDMC is independent of the study team and includes external members with expertise applicable to the study. The eDMC will convene approximately every 6 months until study completion. The eDMC charter describes the role of the eDMC in more detail.

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 (CIOMS) International Ethical Guidelines.
    - Applicable ICH Good Clinical Practice (GCP) Guidelines.
    - **Wording in this paragraph is applicable to study sites in France only:** Prior to enrollment of any participants, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice 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.
    - 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.
- 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.

- 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 sites in Japan please refer to Japan Appendix, Section 10.11.1.4.

- 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 course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his representative will explain the nature of the study to the participant or his legally authorized representative and answer all questions regarding the study.

- 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/IEC or study center.

- The investigator must ensure that each study participant or his 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 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 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 legally authorized representative is fully informed about his right to access and correct his personal data and to withdraw consent for the processing of his 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 ICF(s) during their participation in the study.

- 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 Germany Appendix (Section 10.11.2.3).

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

Two ICFs may be required, one from the Study Site and the other from the Infusion Center (if applicable).

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 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.

10.1.5. Committees Structure

External Data Monitoring Committee (eDMC)

The eDMC is independent of the study team and includes external members with expertise applicable to the study. Further details are provided in the chapter of the eDMC.

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 European Clinical Trials Database (EudraCT), 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 (SOPs).

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

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the European Medicines Agency (EMA) website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

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.

- 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, according to the ICH guidelines, for a minimum of 15 years after study completion unless, clinical study agreement (CSA), 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.

- **Wording in this paragraph is applicable to study sites in France only:** 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.

- 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 Section 10.1.7.

10.1.9. Study and Site Closure

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. 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 sponsor/contract research organization (CRO) 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.

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

- The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.

- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor 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- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.

- For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

- The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

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 investigator site file (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 will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in following table will be performed by the central laboratory unless otherwise indicated in the Table (LL = local lab).
- 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.

Protocol-Required Laboratory Assessments

Assessment	Description		
Hematology	WBC with Differential: • Neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils		RBC • Hemoglobin • Hematocrit • Platelet count
Clinical Chemistry	• Sodium • Potassium • Chloride	• Bicarbonate • Glucose • Phosphate	• Serum creatinine • BUN
Lipid Panel	• LDL • VLDL	• HDL • Triglycerides	• Total Cholesterol
ABO	• ABO group (at Screening if unknown)		
Urinalysis	• pH • Specific Gravity	• Protein • Blood	• Ketones • Glucose
Liver Function Tests (CL & LL)	• Albumin • Total bilirubin • Direct bilirubin • Indirect bilirubin (if available)	• ALP • AST • ALT	• Total Protein • GGT • LDH
Coagulation	• FIX activity (FIX:C), FIX antigen (FIX Ag)		
	Global hemostasis markers • aPTT (in seconds), INR, TAT, TGA, D-dimer		
	• FIX inhibitor testing (Nijmegen Bethesda), (LL if clinically indicated)		
AAV Neutralizing Antibody	• nAb Assay to AAV-Spark 100		
ADA	• Anti-PF-06838435 antibodies (ADA)		
Immunology	• PBMC for ELISPOT • Binding IgG versus IgM antibody response (exploratory)		

Assessment	Description		
Vector Shedding	• Plasma • Urine	• Saliva • Semen	• PBMC
Hepatitis B and Hepatitis C	• Hepatitis B Surface Antigen • Hepatitis B Core AB Total • HBV DNA	• Hepatitis C Virus AB • HCV RNA	
Liver fibrosis	• FibroScan, FibroTest/FibroSURE (including α2-macroglobulin, apolipoprotein A1 and haptoglobin) • APRI		
α-Fetoprotein	• Biomarker for hepatic carcinoma		
HIV Serology	• HIV-1/HIV-2 Antibody Screen		
Viral load and CD4	• HIV-1 Qualitative, RNA		
Spare Plasma (CL)	• Plasma will be stored for repeat or additional testing. These samples will be destroyed at the end of the study		
Factor IX genetic testing)	• Test to be performed if results are not available in the source documents		

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). • 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, as per Section 8.3.

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.

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

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 post-study 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 FIX inhibitor as assessed by Nijmegen assay (≥0.6 Bu/mL, central laboratory).

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

3. Any participant develops hypersensitivity reaction (eg, bronchospasm and anaphylaxis). Infusion site 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 of being related 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 Clinical Trial (CT) Serious Adverse Event (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 52 weeks post-infusion)

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE (including a medically important event – see Section 10.3.2 Definition of SAE, Other Situations)	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy, and occupational exposure	**None**	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 53 post-infusion to EOS)

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE (including a medically important event – see Section 10.3.2 Definition of SAE, Other Situations)	All	All

Non-serious AE • determined to be related to the investigational product by the investigator; • where causality is unknown.	All	None
Exposure to the investigational product under study during pregnancy, and occupational exposure	**None**	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 sponsor in lieu of completion of the sponsor/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer. 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.
- 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 (IB) 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 Pfizer. 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 Pfizer.
- 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". 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

Assessment of Causality
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 Pfizer 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 with a copy of any post-mortem 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 via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor. • 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.

SAE Reporting to Pfizer via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Pfizer 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.

SAE Reporting to Pfizer via an Electronic Data Collection Tool
• 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 sponsor by telephone.

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 is 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.

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 (CSR) 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 6 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 drug-induced liver injury (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 aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (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 (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. 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-06838435 is the potential for T-cell induced hepatocyte destruction. In a subset of participants, presentation of 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 FIX 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 the Phase 1/2a study to respond to intervention with corticosteroids.

10.7. Appendix 7: Bleed and Factor Replacement Regimen Definitions

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 or 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 (three 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.

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.

10.8. Appendix 8: Guidelines for Target Factor IX Levels Based on Bleed Type

Type of Hemorrhage	Circulating Factor IX Activity Required [% or (IU/dL)]	Dosing Interval [hours]	Duration of Therapy [days]
Minor Uncomplicated hemarthroses, superficial muscle, or soft tissue	20-30	12-24	1-2
Moderate Intramuscle or soft tissue with dissection, mucous membranes, dental extractions, or hematuria	25-50	12-24	Treat until bleeding stops and healing begins; about 2 to 7 days
Major Pharynx, retropharynx, retroperitoneum, CNS, surgery	50-100	12-24	7-10

10.9. Appendix 9: Instruments for Patient-Reported Outcomes (PROs)

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

Trial ID: Page 1/7

VISIT X
Centre ID/No.:
Subject No.:
Visit Date: D D M M M Y Y Y Y

HAEM-A- QOL

Questionnaire for Adults

Dear Patient,

We would like to find out how you have been feeling during the past weeks. Please answer the following questions in this questionnaire, which was designed specifically for people with hemophilia.

Please follow the instructions below when answering the questions:

- ⇨ Please read each question carefully.
- ⇨ Think about how things have been for you over the past weeks.
- ⇨ Put an "X" in the box corresponding to the answer that fits you best.
- ⇨ Only mark one box for each question.
- ⇨ There are no right or wrong answers.
- ⇨ It's what you think that matters.
- ⇨ There are some aspects that might not concern you (Sports & Leisure, Family Planning, Work & School, e.g., if you don't work or don't go to school). In such a case, please mark the answer category "not applicable."

All your answers will be treated with the strictest confidence!

Date of completion: __ / __ / __ (month/ day/ year)

Trial ID: Page 2/7

VISIT X

Subject No.: |_|_|_|_|_|_|

1. Here we would like to find out about hemophilia and your PHYSICAL HEALTH

	In the past 4 weeks...	never	rarely	sometimes	often	all the time
1.	... my swellings hurt	☐	☐	☐	☐	☐
2.	... I had pain in my joints	☐	☐	☐	☐	☐
3.	... it was painful for me to move	☐	☐	☐	☐	☐
4.	... I had difficulty walking as far as I wanted to	☐	☐	☐	☐	☐
5.	... I needed more time to get ready because of my condition	☐	☐	☐	☐	☐

2. and now about how you have been FEELING because of your hemophilia

	In the past 4 weeks...	never	rarely	sometimes	often	all the time
1.	... my hemophilia was a burden for me	☐	☐	☐	☐	☐
2.	... my hemophilia made me angry	☐	☐	☐	☐	☐
3.	... I was worried because of my hemophilia	☐	☐	☐	☐	☐
4.	... I felt excluded	☐	☐	☐	☐	☐

HAEM-A-QOL - US/English - Version of 12 Oct 15 - Mapi.
ID042797 / Haem-A-QoL_AU1.1_eng-US.doc

Trial ID: Page 3/7

VISIT X

Subject No.: |_|_|_|_|_|_|

3. How does hemophilia affect your VIEW OF YOURSELF?

In the past 4 weeks...	never	rarely	sometimes	often	all the time
1. ... I envied healthy people my age	☐	☐	☐	☐	☐
2. ... I felt comfortable with my body	☐	☐	☐	☐	☐
3. ... hemophilia made my life more difficult	☐	☐	☐	☐	☐
4. ... I felt different from others because of my hemophilia	☐	☐	☐	☐	☐
5. ... I was able not to think all the time about my hemophilia	☐	☐	☐	☐	☐

4. These questions are about SPORTS AND LEISURE

In the past 4 weeks...	never	rarely	some-times	often	all the time	not applicable
1. ... I had to avoid sports that I like because of my hemophilia	☐	☐	☐	☐	☐	☐
2. ... I had to avoid sports like football	☐	☐	☐	☐	☐	☐
3. ... I played sports just as much as others	☐	☐	☐	☐	☐	☐
4. ... I didn't have the freedom to travel where I wanted	☐	☐	☐	☐	☐	☐
5. ... it was necessary for me to plan everything in advance	☐	☐	☐	☐	☐	☐

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ID042707 / Haem-A-QoL_AU1.1_eng-US.doc

Trial ID: Page 4/7

VISIT X

Subject No.: |_|_|_|_|_|_|

5. These questions are about WORK AND SCHOOL

	In the past 4 weeks...	never	rarely	some-times	often	all the time	not applicable
1.	... I was able to go to work/school regularly in spite of my hemophilia	☐	☐	☐	☐	☐	☐
2.	... I was able to work/study like healthy colleagues	☐	☐	☐	☐	☐	☐
3.	... my everyday work/school activities were jeopardized by my hemophilia	☐	☐	☐	☐	☐	☐
4.	... I found it difficult to pay attention at work/school because I was in pain	☐	☐	☐	☐	☐	☐

6. The next questions are about DEALING WITH HEMOPHILIA

	In the past 4 weeks...	never	rarely	sometimes	often	all the time
1.	... I tried to recognize early on when a bleed developed	☐	☐	☐	☐	☐
2.	... I was able to tell whether or not I was bleeding	☐	☐	☐	☐	☐
3.	... I was able to control my bleeds	☐	☐	☐	☐	☐

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ID042797 / Haem-A-QoL_AU1.1_engUS.doc

Trial ID: Page 5/7

VISIT X

Subject No.: |_|_|_|_|_|_|

7. and what about your TREATMENT?

	In the past 4 weeks...	never	rarely	sometimes	often	all the time
1.	... I was dependent on the factor concentrate because of my hemophilia	☐	☐	☐	☐	☐
2.	... I was dependent on physicians for the treatment of my hemophilia	☐	☐	☐	☐	☐
3.	... I was annoyed about the amount of time spent having the injections	☐	☐	☐	☐	☐
4.	... I felt the injections interrupted my daily activities	☐	☐	☐	☐	☐
5.	... I was afraid of complications	☐	☐	☐	☐	☐
6.	... I had problems with how my treatment was administered	☐	☐	☐	☐	☐
7.	... I was afraid that in case of emergency, other doctors wouldn't know how to treat hemophilia	☐	☐	☐	☐	☐
8.	... I was satisfied with the hemophilia center	☐	☐	☐	☐	☐

HAEM-A-QOL - US/English - Version of 12 Oct 15 - Mapi
ID042797 / Haem-A-QoL_AU1.1_engUS.doc

Trial ID: Page 6/7

VISIT X

Subject No.: |_|_|_|_|_|_|

8. What do you think about the FUTURE?

	Recently...	never	rarely	sometimes	often	all the time
1.	... I have been thinking that it will be difficult for me to lead a normal life	☐	☐	☐	☐	☐
2.	... I have been expecting that things will get better in the future	☐	☐	☐	☐	☐
3.	... I have been worrying that my condition is worsening	☐	☐	☐	☐	☐
4.	... my life plans have been influenced by my hemophilia	☐	☐	☐	☐	☐
5.	... I have been afraid that I will need a wheelchair	☐	☐	☐	☐	☐

9. The next questions are about hemophilia and your FAMILY PLANNING

	Recently...	never	rarely	some-times	often	all of the time	not applicable
1.	... I have had difficulties having children	☐	☐	☐	☐	☐	☐
2.	... I have been afraid that I cannot have children	☐	☐	☐	☐	☐	☐
3.	... I have been afraid that I will not be able to take care of my children	☐	☐	☐	☐	☐	☐
4.	... I worry about not being able to raise a family	☐	☐	☐	☐	☐	☐

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ID942797 / Haem-A-QoL_AU1.1_emp-US.doc

Trial ID: Page 7/7

VISIT X

Subject No.: |_|_|_|_|_|_|

10. What about PARTNERSHIP AND SEXUALITY?

	Recently...	never	rarely	sometimes	often	all the time
1.	... I have been finding it difficult to date because of my hemophilia	☐	☐	☐	☐	☐
2	... I have been insecure in my intimate relationships because of my hemophilia	☐	☐	☐	☐	☐
3.	... I haven't been able to have a normal relationship because of my hemophilia	☐	☐	☐	☐	☐

THANK YOU FOR YOUR ASSISTANCE!

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10.9.2. Hemophilia Activities List (HAL)

UMC Utrecht
Van Creveldkliniek

Hemophilia Activities List

Date	: .....
Patient ID	: .....

Version 2.0 2015

When using this questionnaire, please use the following references:

Van Genderen FR, Van Meeteren NLU, Van der Bom JG, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM. Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List. *Haemophilia* 2004; **10**: 565-71.

Van Genderen FR, Westers P, Heijnen L, De Kleijn P, Van den Berg HM, Helders PJM, Van Meeteren NLU. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List (HAL). *Haemophilia* 2006; **12**: 36-46.

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Introduction

This is the Hemophilia Activities List, or HAL. In this questionnaire several activities are listed that could be difficult for adults who have hemophilia. The aim of this questionnaire is to see how easy it is for you to do these activities.

General comments

*When answering the questions, it is only **your own** experience that counts. For every activity, you are asked whether you had any difficulty in performing that activity **due to hemophilia**. There are seven different response options. Answer each question by placing an "X" in the box that describes your situation.*

Example:

In the past month, did you have any difficulty **due to hemophilia** with:

		n/a	Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Using public transportation (bus, train, subway, streetcar)	□ 8	□ 1		□ 2	□ 3	□ 4	□ 5	□ 6

Please choose only one box per question. The "N/A" response option ("not applicable") can be used if you never (had to) perform that specific activity. The "N/A" option is only available for some activities. The difference between the "Impossible" and "Always" response option, is that with "Always" you were in fact able to perform that activity, but with problems and with "Impossible" you are unable to perform that activity.

It is very important that you answer all questions. Even when a question seems irrelevant to you, or when you have no opinion relating to the question, please mark the box that describes your situation most closely.

It will take 5-10 minutes to finish this questionnaire.

V2.0, 2015 – USA/Canadian		Van Creveldkliniek

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Lying down/sitting/kneeling/standing

In the previous month, did you have any difficulty, due to hemophilia, with:

		Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Sitting down (e.g. on a chair or couch)	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Standing up from a chair *that has* armrests	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Standing up from a chair *that does not* have armrests	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Kneeling/squatting	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Bending forward	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Kneeling for long periods of time	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Squatting for long periods of time	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Standing for long periods of time	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Legs

In the previous month, did you have any difficulty, due to hemophilia, with:

			Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Walking short distances (less than 0.6 miles/less than 15 minutes)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Walking long distances (more than 0.6 miles/more than 15 minutes)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Walking on a soft surface (e.g. on the beach)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Walking on an uneven surface (e.g. cobblestones, high sidewalks)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Strolling/(window-)shopping		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Walking *up* a flight of stairs (a flight of stairs is approximately 14 steps)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Climbing *down* a flight of stairs		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Running (e.g. in order to catch the bus)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Jumping		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Arms

In the previous month, did you have any difficulty, due to hemophilia, with:

			Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Lifting heavy objects		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Carrying heavy objects in the arms		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Fine hand movements (e.g. doing up buttons)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Reaching above your head (to pick something up from a high shelf)		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Use of transportation

In the previous month, did you have any difficulty due to hemophilia, with:

		n/a	Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Riding a bicycle	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Getting in and out of a car	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Using public transportation (bus, train, subway)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Self care

In the previous month, did you have any difficulty due to hemophilia, with:

			Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Drying your whole body		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Putting on a shirt, sweater etc.		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Putting on socks and shoes		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Putting on a tie or closing the top button of a shirt		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Going to the toilet		☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

Household tasks

In the previous month, did you have any difficulty, due to hemophilia, with:

		n/a	Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Going out shopping (for food, drink etc.)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Washing the dishes, cleaning the sink	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Cleaning the house	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Other household tasks (ironing, making the beds)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Doing odd jobs (both in and around the house)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Gardening	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

V2.0, 2015 – USA/Canadian		Van Creveldkliniek

Hemophilia Activities List		UMC Utrecht Van Creveldkliniek

Leisure activities and sports

In the previous month, did you have any difficulty due to hemophilia with:

		n/a	Impossible		Always a problem	Mostly a problem	Sometimes a problem	Rarely a problem	Never a problem
	Playing games (outdoors, e.g. with your children)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Sports	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Going out (theatre/museum/ movie theatre/bar)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Hobbies	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Dancing	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Going on a vacation (active)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
	Going on a vacation (“passive”; beach-/hotel holiday)	☐ 8	☐ 1		☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

10.9.3. Patient Global Impression of Change - Hemophilia (PGIC-H)

Instructions: For the question below, please select the response that best describes your impression since the start of the study.

Since the start of the study, my life with hemophilia has:

- ☐ Greatly improved
- ☐ Moderately improved
- ☐ Slightly improved
- ☐ Not changed
- ☐ Slightly worsened
- ☐ Moderately worsened
- ☐ Greatly worsened

10.9.4. Hemophilia Life Impacts Questionnaire (HLIQ)

OVERALL INSTRUCTIONS:

The following questions ask about the ways that living with AND treating hemophilia has affected your life during the past week. There are no right or wrong answers. Please select the response that best represents your experience.

ITEMS 1-7 INSTRUCTIONS:

Please answer these first 7 questions thinking specifically about your experience **living with and treating your hemophilia**.

1. During the past week, how much was your **hemophilia on your mind**?

Not at all	A little	Somewhat	Quite a bit	Constantly
□	□	□	□	□

2. During the past week,

   a. Did you take any **precautions because of your hemophilia**? (*Gate Question*)

      □ Yes (Go to 2b)

      □ No (Stop)

   b. If 2a = Yes

During the past week, how much **precaution** did you take because of your hemophilia?

A little	Some	Quite a bit	A lot
□	□	□	□

3. During the past week, how much did having hemophilia **interfere with your ability to perform day-to-day activities** (eg, at home, work or school)?

Not at all	A little	Somewhat	Quite a bit	Extremely
□	□	□	□	□

4. During the past week, how much did having hemophilia **limit your ability to live the life you want to live**?

Not at all	A little	Somewhat	Quite a bit	Extremely
□	□	□	□	□

5. During the past week,

   a. Did you participate in any **social activities** (eg, with friends and/or family)? (*Gate Question*)

      □ Yes (*Go to 5c*)

      □ No *(Go to 5b)*

   b. *If 5a = No*

      You answered that you did not participate in any **social activities,** was this:

      □ Due to having hemophilia (*Stop*)

      □ Due to other reasons (*Stop*)

   c. If 5a = Yes

During the past week, how much did having hemophilia **interfere with your ability to participate in social activities** (eg, with friends and/or family)?

Not at all	A little	Somewhat	Quite a bit	Extremely
□	□	□	□	□

6. During the past week,

   a. Did you participate in any **hobbies or leisure activities**? (*Gate Question*)

      □ Yes (*Go to 6c*)

      □ No (*Go to 6b*)

b. *If 6a = No*

You answered that you did not participate in any **hobbies or leisure activities**, was this:

□ Due to having hemophilia (*Stop*)

□ Due to other reasons (*Stop*)

c. If 6a = Yes

During the past week, how much did having hemophilia **interfere with your ability to participate in hobbies or leisure activities**?

Not at all	A little	Somewhat	Quite a bit	Completely
□	□	□	□	□

7. During the past week,

a. Did you participate in any **physical activities** (eg, exercise or sports**)**? (*Gate Question*)

□ Yes (*Go to 7c*)

□ No (*Go to 7b*)

b. *If 7a = No*

You answered that you did not participate in any **physical activities (eg, exercise or sports),** was this:

□ Due to having hemophilia (*Stop*)

□ Due to other reasons (*Stop*)

c. If 7a = Yes

During the past week, how much did having hemophilia **interfere with your ability to participate in physical activities** (eg, exercise or sports)?

Not at all	A little	Somewhat	Quite a bit	Completely
□	□	□	□	□

ITEMS 8 & 9 INSTRUCTIONS:

Please answer these last 2 questions thinking specifically about your experience **with treating your hemophilia**.

8. During the past week, how difficult was it to **fit hemophilia treatment into your life**?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. During the past week, how much did **treating your hemophilia interfere with your ability to enjoy life**?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐	☐	☐	☐	☐

10.9.5. EQ-5D-5L Questionnaire

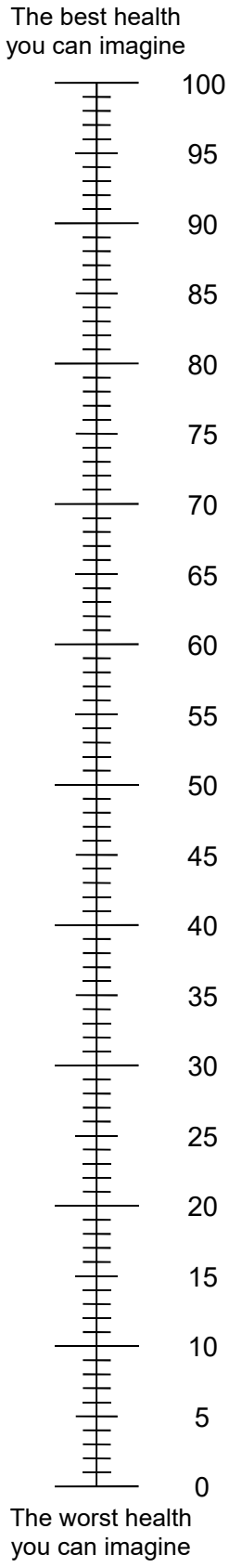
Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.	
MOBILITY	
I have no problems walking	☐
I have slight problems walking	☐
I have moderate problems walking	☐
I have severe problems walking	☐
I am unable to walk	☐
SELF-CARE	
I have no problems washing or dressing myself	☐
I have slight problems washing or dressing myself	☐
I have moderate problems washing or dressing myself	☐
I have severe problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
USUAL ACTIVITIES *(eg, work, study, housework, family or leisure activities)*	
I have no problems doing my usual activities	☐
I have slight problems doing my usual activities	☐
I have moderate problems doing my usual activities	☐
I have severe problems doing my usual activities	☐
I am unable to do my usual activities	☐
PAIN/DISCOMFORT	
I have no pain or discomfort	☐
I have slight pain or discomfort	☐
I have moderate pain or discomfort	☐
I have severe pain or discomfort	☐
I have extreme pain or discomfort	☐
ANXIETY/DEPRESSION	
I am not anxious or depressed	☐
I am slightly anxious or depressed	☐
I am moderately anxious or depressed	☐
I am severely anxious or depressed	☐
I am extremely anxious or depressed	☐

• We would like to know how good or bad your health is TODAY.
• This scale is numbered from 0 to 100.
• 100 means the best health you can imagine. 0 means the worst health you can imagine.
• Mark an X on the scale to indicate how your health is TODAY.
• Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.10. Appendix 10: Non-Inferiority Margin Selection

The choice of the non-inferiority margin is based on the consideration of the following guidelines. The constancy assumption was taken into consideration and the "95%-95%" method is used.

- FDA guideline for selecting a margin based on historical data.[28]
- EMA guidelines on the choice of non-inferiority margin.[29]
- International Conference on Harmonization (ICH) Note for Guidance E9 (Statistical Principles for Clinical Trials).[30]
- ICH Note for Guidance E10 (Choice of Control Group).[31]
- CPMP Points to Consider on Switching Between Superiority and Non-Inferiority.[32]

The non-inferiority margin will be based on the effect of prophylaxis treatment over on-demand treatment (as the reference treatment). This will be expressed via a mean difference in ABR in a single arm trial with a switch from on-demand to prophylaxis using a paired comparison. This design reflects the Committee for Medicinal Products for Human (CHMP) guidance for the design of prophylaxis clinical trials. Based on the lower bound of the confidence interval of an estimate for the ABR for treated bleeds (referred to as ABR_{treat}) in on-demand participants, the ABR_{treat} is assumed to be higher by at least CCI, which will be considered as M_1 in the non-inferiority test setting for the ABR_{treat}. It is assumed that the treatment difference (on-demand – prophylaxis) in ABR_{total} is proportional to that in ABR_{treat}. The ratio of the treatment difference (ABR_{total} over ABR_{treat}) is estimated to be CCI .[33,34] Thus M_1 for ABR_{total} is estimated to be CCI .

Given the large effect size of prophylaxis treatment (over on-demand therapy), an appropriate value for M_2 will be considered in order to preserve a sufficiently large proportion of this effect. Simulations have been conducted to assess preservation levels of CCI of M_1. These percentages correspond to non-inferiority margin values of CCI bleeding events/year respectively, on an absolute scale. A value of 3.0 for M_2 (approximately CCI of the M_1 effect preserved) is proposed as both clinically meaningful and yielding a reasonable sample size for establishing efficacy.

"The choice of delta must always be justified on both clinical and statistical grounds. It always needs to be tailored specifically to the particular clinical context and no rule can be provided that covers all clinical situations".[29] In the sponsor's BeneFix study 3090A1-400, which included 50 adult hemophilia B patients to compare prophylaxis efficacy results for this FIX product on different regimen in the clinical trial setting, ABR_{treat} was estimated to range from CCI . "A separate study compared recombinant factor IX Fc fusion protein (rFIXFc, Alprolix; Biogen Inc. Cambridge, MA USA). The ABR_{treat} of the prophylaxis regimen are 3.0 and 1.4".[35] In a "European retrospective study of real-life haemophilia treatment", the mean ABR_{treat} observed of prophylaxis regimen in different European countries range from 1.7 to 6 for haemophilia B severe patients.[36] From the experience with

Hemlibra (emicizumab-kxwh; Genentech, Inc. South San Francisco CA), the ABR_{total} ranged from 2.5 (HAVEN-1 study) to 5.5 (HAVEN-3 study). The HOPE-B trial result for AMT-061 showed an ABR_{total} of 1.51 (EAHAD 2022).[37] Given a difference of [redacted] between the prospectively assessed ABR_{treat} in the real world setting and in the clinical trial setting, and a difference of [redacted] in ABR_{total}, and allowing for modest differences in the respective study populations, the sponsor feels a value of 3.0 represents a reasonably conservative margin of non-inferiority.

10.11. Appendix 11: Country-specific Requirements

10.11.1. Japan Appendix

This appendix is only for Japanese investigators at Japanese sites.

10.11.1.1. Study Intervention Defects Definitions (per Japanese regulations)

- **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.

10.11.1.2. Reporting Criteria

All study intervention defects are to be reported to the sponsor within 24 hours of investigator awareness (see Section 10.11.1.3) 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.

10.11.1.3. 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.

10.11.1.4. Japan Specific Protocol Wording

Protocol Section 5.2. Exclusion Criteria
Other Exclusions
The text with underline was added.

19. Sensitivity to any of the study interventions, or components thereof***, or bovine-derived component***, or drug or other allergy that, in the opinion of the investigator or the sponsor's medical monitor, contraindicates participation in the study.

Protocol Section 6.4. Study Intervention Compliance
The text with underline was added.

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

Protocol Section 8. STUDY ASSESSMENTS AND PROCEDURES
Day 1 (at Study Site or at approved Infusion Center)
The text with underline was added after the last paragraph

Japanese participants enrolled at Japanese sites must be hospitalized on IP infusion day and their condition must be closely monitored at the study site through next day after the IP administration for ensuring the participant safety. The necessity of hospitalization thereafter should be determined by the principal investigator according to the participant's condition.

Protocol Section 8.3.4. Regulatory Reporting Requirements for SAEs
The text with underline was added.

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

Protocol Section 10.1.1. Regulatory and Ethical Considerations
The text with underline was added.

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.

10.11.2. Germany Appendix

This appendix is only for sites in Germany.

10.11.2.1. Section 5.1 Inclusion Criteria

6. 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.

10.11.2.2. Section 5.2 Exclusion Criteria

16. 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.

17. Unable to comply with scheduled visits, treatment plan, laboratory tests and other study procedures for up to six years post-infusion of PF-06838435 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**.**

10.11.2.3. 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.

10.11.2.4. Section 1.3. Schedule of Activities (SoA)

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

10.11.2.5. Section 8.1.2.3. X-ray Assessments to Evaluate Joints

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

10.12. Appendix 12: Hemophilia Joint Health Score

The Hemophilia Joint Health Score 2.1 worksheet can be found in Feldman et al (2011).[38]

Subject ID #:_____ **Name of Physiotherapist:**_____

Assessment # : _____ **Date:** _____
yyyy / mm / dd

Time: _____

Hemophilia Joint Health Score 2.1 - Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension Loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals _____ NE = Non-Evaluable

Global Gait Score + _____

(☐ NE included in Gait items)

HJHS Total Score = _____

Swelling
0 = No swelling
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Extension loss
(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11°- 20°
3 = > 20°

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity with maximum resistance (gr.5)
1 = Holds test position against gravity with moderate resistance (but breaks with maximal resistance) (gr.4)
2 = Holds test position with minimal resistance (gr. 3+), or holds test position against gravity (gr.3)
3 = Able to partially complete ROM against gravity (gr.3-/2+), or able to move through ROM gravity eliminated (gr.2), or through partial ROM gravity eliminated (gr.2-)
4 = Trace (gr.1) or no muscle contraction (gr.0)
NE = Non-evaluable

Global Gait (walking, stairs, running, hopping on 1 leg)
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-evaluable

NOTE: There is an accompanying instruction manual and worksheets that are required when administering the HJHS

General Comments:

_____
_____
_____
_____

The HJHS is designed for use by physiotherapists. In order to maintain the precision and validity of the tool (score), the developers of the tool 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 assessment and specifically administration of the HJHS.

It is essential for the physiotherapist to possess the required expertise and skills necessary to use anthropometric measures such as muscle testing and range of motion /goniometry, as well as posture & gait assessment prior to performing the evaluation (HJHS).

10.13. Appendix 13: 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).

10.13.1. Alternative Study Procedures During COVID-19 Pandemic

10.13.1.1. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. In the event that an on-site clinic visit or unscheduled on-site clinic visit cannot be conducted after Day 1, study sites are permitted to defer the conduct of the procedures, listed below, to the mobile phlebotomy/ home health services, provided that local regulations permit:

- All protocol required lab draws
- Weight and vital signs (eg, body temperature, BP, pulse rate, respiratory rate)
- Patient-Reported Outcomes (PROs)

In the event that an on-site clinic visit cannot be completed, it is understood that the procedures, like the ones listed below, may not be able to be performed. In such cases, you should document the reason for the missed test (eg, on-site clinic visit missed due to COVID-19 restrictions).

- Physical exam
- Electrocardiogram
- Target Joint Assessment
- Liver Ultrasounds
- Hemophilia Joint Health Score (HJHS)
- Joint X-ray (Optional)
- Joint MRI (Optional)

10.13.1.2. 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 by phone contact. Video contact can be used if permitted by local regulations. During the phone (or video) contact, the following assessments should be performed:

- Review and record any new concomitant medications or changes in concomitant medications since last contact;

- Review and record any AEs and SAEs since last contact, including but not limited to COVID-19 related events. The AE and SAE reporting process should be followed per protocol (Section 10.3, Appendix 3);
- Review bleeding episodes and FIX infusions reported in the eDiary.

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

10.13.1.3. Guidelines for Capturing Post-Infusion Procedures

In the event that any of the post-infusion 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 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 deviations.

- ECG
- Liver ultrasound
- HJHS
- Global Hemostasis Markers

10.13.2. Alternative Study Procedures For Extenuating Circumstances

In the event of extenuating circumstances, the same mitigations that were put in place for the COVID-19 pandemic, see Section 10.13.1, will be used for the duration of the trial.

10.13.3. Participants Who Test Positive for COVID-19

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 medication when he has **no COVID-19 symptoms for 10 days** and:

- tests negative for COVID-19

Or

- continue to test positive for COVID-19, but at least 21 days after the earliest COVID-19 positive 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 etc., if applicable)

And

- consult with the sponsor.

10.13.4. COVID-19 Vaccination Guidelines

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 investigational product, it is recommended that the infusion of the investigational product 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 investigational product, the COVID-19 vaccine may be administered once the patient has reached at least 12 weeks of follow-up post-investigational product infusion if the participant is not currently on corticosteroids. If the participant is on corticosteroids at 12 weeks post-infusion, it is recommended to delay vaccination until the participant has been weaned off corticosteroids.

2. It is recommended that WFH guidelines be followed 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 for any questions concerning COVID-19 vaccination and study participants.

4. COVID-19 vaccinations should be reported as a concomitant medication on the case report form (CRF).

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

10.14. Appendix 14: 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 2	**12 October 2021**	The primary reason for Amendment 2 is to change the analysis period for the co-primary endpoints and the key secondary endpoints based on FDA feedback that analysis be performed 12 months post-steady state versus 12 months post-infusion.
		• For co-primary endpoints and key secondary endpoints, 12 months updated to 15 months in Synopsis (Section 1.1), Schema (Section 1.2), Objectives, Estimands and Endpoints (Section 3), Estimands and Statistical Hypotheses (Section 9.1), Sample Size Determination (Section 9.2), and Efficacy Analyses (Section 9.4.1). Additionally, all bleeding related secondary efficacy endpoints were updated from 12 months to 15 months in Objectives, Estimands and Endpoints (Section 3) and Efficacy Analyses (Section 9.4.1). • Extended the time period for any participant with a planned surgical procedure requiring FIX surgical prophylactic factor treatment from 12 to 15 months in Exclusion Criterion #10 (Section 5.2). Removal of planned interim analysis (Sections 9.4, 9.4.1, and 9.5), clarified primary endpoint of ABR is for treated bleeds (Sections 1.1, 3, 9.1.1, and 9.4.1), added ABR for total bleeds (treated and untreated) as a key secondary objective and endpoint (Sections 1.1, 1.2, 3, 9.1.1, and 9.4.1), and clarified the efficacy of PF-06838435 in terms of the use of exogenous FIX in the key secondary endpoints (Sections 1.1 and 3) based on evolving regulatory expectations. Added allowed therapies including COX-2 inhibitors and topical NSAIDs, where medically necessary, and HIV therapy (Section 6.5.1), and clarified low dose aspirin and PRN/short-term use of NSAIDs may be used where medically necessary (Section 6.5.2). Added guidance in the event that a participant is unable to provide any semen for vector shedding over the course of 1 month post IP infusion in Samples for Vector Shedding Assays (Section 8.5.1). Incorporated clarifications previously communicated by PACL #7: • Guidance regarding the inclusion of participants who test positive for COVID-19 was added within the

Amendment 2	**12 October 2021**	The primary reason for Amendment 2 is to change the analysis period for the co-primary endpoints and the key secondary endpoints based on FDA feedback that analysis be performed 12 months post-steady state versus 12 months post-infusion.
		Alternative Measures During Public Emergencies Appendix (Section 10.13) and references to this guidance were added in Schedule of Activities (Section 1.3), Preparation/Handling/Storage/Accountability (Section 6.2), Study Intervention Compliance (Section 6.4), and Study Assessments and Procedures (Section 8). • Guidance regarding COVID-19 vaccination was added within the Alternative Measures During Public Emergencies Appendix (Section 10.13) and references to this guidance were added in Schedule of Activities (Section 1.3), Preparation/Handling/Storage/Accountability (Section 6.2), Study Intervention Compliance (Section 6.4), Concomitant Therapy (Section 6.5), Disallowed Therapy (Section 6.5.2), and Study Assessments and Procedures (Section 8). • Addition of language regarding missed assessments to Study Assessments and Procedures (Section 8) and Alternative Measures During Public Emergencies Appendix (Section 10.13). • Minor typographical correction to HIV Exclusion Criterion #15 (Section 5.2). • Language regarding use of mobile phlebotomy/home health services and pre-dose LFT blood clarified in Schedule of Activities (Section 1.3).

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		Revisions and additions were made per Germany, Japan and France Ethics Committee and/or regulatory authority (RA) requirements. The following sections were affected:
		
		• Objectives, Estimands and Endpoints
		
		  • Estimands wording was revised for clarity per German Ethics Committee.
		
		• Inclusion/Exclusion Criteria
		
		  • Inclusion Criterion #6 was revised to meet German Ethics Committee required language in Section 10.11.2.1.
		
		  • Exclusion Criteria #16 and #17 were revised to meet German Ethics Committee required language in Section 10.11.2.2.
		
		  • Exclusion Criterion #19 was revised to meet Japan required language in Section 10.11.1.4.
		
		• Preparation/Handling/Storage/Accountability
		
		  • Regulatory and Ethical Considerations was revised with language applicable to study sites in France.
		
		• Study Intervention(s) Administered
		
		  • Reference was added to new country-specific language in Section 10.11.
		
		• Study Assessments and Procedures
		
		  • References to new country-specific language in Section 10.11 were added.
		
		• Adverse Events and Serious Adverse Events
		
		  • References to new country-specific language in Section 10.11 were added.
		
		• Pharmacokinetics
		
		  • For clarity and flexibility and as a country-level request (Germany), it was added that as FIX inhibitors or T-cell mediated immune response may impact the FIX activity levels,

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		this information will also be taken into account while deriving FIX:C activity levels.
		
		• Statistical Considerations
		
		  • Clarifications were made in the text describing hypothesis testing as a country-level request (Germany).
		
		  • Revisions and updates were made to provide clarification in estimands and statistical hypotheses, populations for analyses, efficacy analyses and interim analyses according to German Ethics Committee required language.
		
		• Appendices
		
		  • Regulatory and Ethical Considerations was revised with language applicable to study sites in France.
		
		  • Cross references were added to appropriate sections for new German-specific and Japan-specific language.
		
		  • A country-specific requirements appendix was added for Japan as Section 10.11.1 as per Japanese RA requirement.
		
		  • A country-specific requirements appendix was added for Germany as Section 10.11.2 as per German regulations and RA requirements.
		
		PGIC-H was removed from endpoints. This was a correction as PGIC-H is not an endpoint but is an anchor measure used to assist with the interpretation of the PRO endpoints. The following sections were affected:
		
		• Objectives, Estimands and Endpoints
		
		  • PGIC-H was removed from Objectives and Endpoints table.
		
		• Statistical Considerations
		
		  • PGIC-H was removed from secondary efficacy analysis endpoints.

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		Blood for LFTs is now required (rather than recommended) to be drawn and tested locally and centrally up to 3 days prior to Day 1 dosing, and reviewed prior to thawing drug, as these LFT results may help in the assessment of future LFTs and decisions on when to begin corticosteroid treatment, if necessary. The following sections were affected:
		
		• Schedule of Activities for Year 1
		
		  • Table headers and notations were revised
		
		  • Study Assessments and Procedures
		
		To align with data capture guidance and SAE process, AEs and SAEs that begin after obtaining informed consent but before the start of study intervention must now be recorded on the AE section of the CRF, not the Medical History/Current Medical Conditions section. The following sections were affected:
		
		• Time Period and Frequency for Collecting AE and SAE Information
		
		  • Text was removed stating that medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
		
		  • Text was added describing AE/SAE collection details in case of participant discontinuation.Text was added that all nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent, will be recorded on the AE section of the CRF.
		
		  • A statement was added that the investigator is to record on the CRF directly observed and spontaneously reported AEs and SAEs per details provided in Section 10.3.3.
		
		It was recommended that participants who are initiated on corticosteroid treatment be treated with an acid reducer for

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).
		the duration of the corticosteroid course. The following sections were affected: • Schedules of Activities for Year 1 and Year 2 to Year 6 ◦ Study Assessments and Procedures • Adverse Events and Serious Adverse Events ◦ Analysis of Cellular Immune Response by ELISPOT (enzyme linked immune-spot) ◦ Immunomodulation Optimization (Presumed T-Cell Activation) Corrections, clarifications and revisions for consistency were made. The following sections were affected: • Schedules of Activities for Year 1 and Year 2 to 6 ◦ Table headers and notations were revised, added and removed as appropriate for clarity, consistency, as corrections and for flexibility. • Introduction ◦ Correction regarding female carriers was made in the Overview of Hemophilia B. ◦ Correction was made to target joint definition. ◦ Clarifications were made in the Gene Transfer Therapy in Hemophilia sub-section. • Objectives, Estimands and Endpoints ◦ Wording within primary and secondary endpoint and additional tertiary objective and endpoint sections were corrected and revised for clarity. • Inclusion/Exclusion Criteria ◦ Inclusion Criterion #1 was revised as participants would have met these requirements in C0371004 before entering C0371002, and to add clarity regarding when

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).
		the 6 months of routine FIX prophylaxis should be completed. • Inclusion Criterion #2 was corrected to specify that participants should have documented moderately severe to severe hemophilia B, defined as FIX:C ≤2%. • Exclusion Criteria #1, 6, 7 and 8 were revised for clarity. • Inclusion Criterion #4 was corrected as creatinine ≤2.0 mg/dL. • Exclusion Criterion #8 was revised to clarify specifics of repeat testing. • Exclusion Criterion #12 was corrected to specify that participants previously dosed in a gene therapy research trial would be excluded. • Lifestyle Considerations • 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 • Text was updated and revised for consistency with updates in Exclusion Criterion #8. • Study Intervention(s) Administered • Updated for clarity and consistency. • Concomitant Therapy • Clarified that information regarding surgeries (eg, blood loss and/or transfusion amounts) will be collected on relevant CRF(s) throughout the study.

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).
		• Disallowed therapies were clarified. • Participant Discontinuation/Withdrawal from the Study • Clarified language to the Participant Discontinuation/Withdrawal from Study section and added Section 7.2.1 to clarify instructions to be followed when a participant withdraws consent. • Study Assessments and Procedures • Text was updated and revised for consistency with updates in the Schedules of Activities. • Efficacy Assessments • Text was added to clarify process to follow if bleeding episodes or treatments are not entered in the eDiary during the appropriate time window. • The title of the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) was corrected as needed in this section and throughout the document. Domain names for the Haem-A-QoL were updated to be consistent with the development publication. • Statements were added for consistency with the SoAs in the MRI to Evaluate Joints and X-Ray Assessments to Evaluate Joints sub-sections. • Safety Assessments • Vital signs were revised from “oral temperature” to “body temperature” to permit flexibility with methods utilized by the sites. • Vital signs were revised from **upright** position to **upright/sitting** position for clarity. • Clinical laboratory assessments language was revised to remove redundancy and for clarity.

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		• Section 8.2.5 Liver Ultrasound was added to clarify that all participants will undergo liver ultrasound imaging and details of the ultrasound acquisition will be provided in a separate scanning guide.
		
		• Adverse Events and Serious Adverse Events
		
		  • Events of special interest was replaced with adverse events of special interest.
		
		  • Correction was made to specify that central laboratory, rather than the sponsor, may make a determination as to whether any FIX Inhibitor samples have been compromised.
		
		  • Text was revised to clarify and more clearly describe exposure during pregnancy, breastfeeding and occupational exposure and reporting requirements.
		
		  • Text was revised to clarify volume required for analysis of anti-PF-06838435 antibodies and neutralizing anti-PF-06838435 antibodies.
		
		  • Section 8.3.6.1.1 was added to describe Immunology Exploratory sampling.
		
		  • Wording was revised regarding immunomodulation optimization (for participants who develop hepatitis transaminitis) to more clearly describe elevations in liver transaminases and to eliminate any potential delays in initiating corticosteroid treatment.
		
		  • Not performing a flush of the IV line at conclusion of the IP infusion was added to list of medication errors.
		
		  • It was clarified that the sponsor must be notified within 24 hours when there is medication dosing error.
		
		  • New subsection, Adverse Events of Special Interest, was added, AESIs were defined, and AESIs replaced events of special interest.

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		• Pharmacokinetics
		  • Time allowance windows were added for samples for vector shedding assays for clarity, and the specific volume of samples was removed. The specific amounts to be collected are included in one place (ie, the laboratory manual).
		• Appendices
		  • Text describing results posted to www.clinicaltrials.gov and EudraCT was revised for clarity and flexibility.
		  • Clinical Laboratory Tests table was revised for consistency and minor corrections were made.
		  • Definition of AE was revised for consistency with revisions in protocol body, to include medically important events in the definition of SAE.
		  • Definition of SAEs added guidance that a suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic is considered serious.
		  • Text describing events of special interest were removed from Definition of SAE.
		  • Additional clarity was added to Recording/Reporting and Follow up of AEs and/or SAEs during the Short-Term and Long-Term Monitoring Periods in Section 10.3.3.
		  • Appendix 4 text regarding exposure during pregnancy was removed as this is now included in Section 8.3.5.1.
		  • Appendix 7 heading was revised to Bleed and Factor Replacement Regimen Definitions and text was clarified in the appendix. Definitions of Factor Replacement Regimens, Prophylaxis Therapy, Preventative Therapy and On-Demand Therapy were added for clarity.

Amendment 1	**23 June 2020**	The main reason for Amendment 1 is to incorporate changes requested by German Ethics Committee and incorporate clarifications previously communicated by protocol administrative change letters (PACLs).

		• References
		  • Reference #6 and 26 were corrected, and #23 was moved up to #13 per the citation, and references were re-numbered accordingly.
		
		Text was added per current COVID-19 guidelines. The following sections were affected:
		
		• Schedules of Activities for Year 1 and Year 2 to Year 6
		  • A statement was added above each table referring to a new appendix with guidance for alternative study visit information.
		
		• Study Assessments and Procedures
		  • Investigators were provided with steps to take when circumstances outside their control may make it unfeasible to perform protocol-specified tests and procedures.
		
		• Section 10.13, Appendix 13
		  • New appendix was added describing alternative study procedures during COVID-19 pandemic.
		
		The Protocol Summary was revised as appropriate for consistency with changes in the body of the document.

Editorial, grammatical, formatting and administrative changes were made throughout the document, including changes to the List of Abbreviations.		
Original Protocol	13 December 2018	Not applicable

10.15. Appendix 15: Abbreviations

AAV	adeno-associated virus
ABR	annualized bleeding rate
ABR_{total}	annualized bleeding rate for total bleeds (treated and untreated)
ABR_{treat}	annualized bleeding rate for treated bleeds
ADA	anti-drug antibody
AE	adverse event
AIR	annualized (FIX) infusion rate
ALP	alkaline phosphatase
ALT	alanine transaminase
APRI	AST to platelet ratio index
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BP	blood pressure
BU	Bethesda Units
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation or classification determinant
CFR	Code of Federal Regulations
CL	central laboratory
COVID-19	coronavirus disease of 2019
COX-2	cyclooxygenase-2
CPT	cell preparation tube
Cr	creatinine
CRF	case report form
CRO	Contract Research Organization
CSA	clinical study agreement
CT	clinical trial
CTA	Clinical Trials Agreement
DILI	drug-induced liver injury
dL	deciliter

DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
eDMC	external data monitoring committee
DRE	disease related event
EAHAD	European Association for Haemophilia and Allied Disorders
ECG	electrocardiogram
EDP	exposure during pregnancy
EHC	European Haemophilia Consortium
EMA	European Medicines Agency
EOS	end of study
EQ-5D-5L	EuroQol, 5 dimensions, 5 levels
EU	European Union
FDA	U.S. Food and Drug Administration
FIX	coagulation factor IX
FIX Ag	coagulation factor IX antigen
FIX:C	factor IX: circulating
GCP	Good clinical practice
GGT	gamma-glutamyl transferase
H2	histamine type 2
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HLIQ	Hemophilia Life Impacts Questionnaire
hr	hour/s
HRT	hormonal replacement therapy

ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IND	Investigational New Drug
INR	international normalized ratio
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
ISF	investigator site file
ITT	Intent to Treat
IU	international units
IV	intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDH	lactic acid dehydrogenase
LFT	liver function tests
LL	local laboratory
min	minute/s
MRI	magnetic resonance imaging
nAb	neutralizing antibodies
NE	non-evaluable
NHF	National Hemophilia Foundation
NI	non-inferiority
NIMP	non-investigational product
NSAIDs	non-steroidal anti-inflammatory drugs
PACL	protocol administrative change letter
PBMC	peripheral blood mononuclear cells
PCD	primary completion date
PGIC-H	Patient Global Impression of Change - Hemophilia
PPI	proton pump inhibitor

PRN	pro re nata
PROs	Patient-Reported Outcomes
NHP	nonhuman primate/s
QALY	Quality Adjusted Life Year
QTc	corrected QTc interval
rAAV	recombinant adeno-associated viral vector
RA	regulatory authority
RBC	red blood cell
rFIXFc	recombinant factor IX Fc fusion protein
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SJ-UCL	St. Jude Children's Research Hospital and University College London
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reactions
TAT	thrombin-antithrombin level
TBili	total bilirubin
TGA	thrombin generation assay
ULN	upper limit of normal
VAS	visual analog scale
VRS	verbal rating scale
Vg	vector genome
WBC	white blood cell
WFH	World Federation of Hemophilia
WOCBP	woman of childbearing potential

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