Protocol Title: Gene therapy, Open-label, Dose-escalation Study of PF-06838435 (SPK-9001) [adeno-associated viral vector with human factor IX gene] in subjects with hemophilia B

Protocol Number: C0371005/previously SPK-9001-01

Amendment Number: 7

Compound Number: PF-06838435/previously SPK-9001

Product name: Fidanacogene elaparvovec

Study Phase: Phase 1/Phase 2a

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

Regulatory Agency Identifier Number(s)

Registry	Identification (ID)
Investigational New Drug (IND) Number	CCI [redacted]

Approval Date: 14 June 2019

[redacted]

[redacted]

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY

Document	Date
Amendment 6.0 1. Clarification for Exclusion Criteria #1, #3, and #4. 2. Clarification to the Schedule of Activities footnotes. 3. Administrative changes throughout. 4. Removal of reference to the Immunosuppressive Therapy Dosing Committee as it was never formed. 5. Addition of Table 1: Laboratory assessments and location for analysis.	29-Sep-2017
Amendment 5.1 1. Modified Dose Level Expansion parameters. 2. Updated FibroScan score. 3. Updated Schedule of Activities, removed requirement for FIX incremental recovery at Week 52/EOS, added the following: collection of joint health assessments and clarified target joint assessments, pain and activity questionnaires, Week 52/EOS urinalysis, liver ultrasound. 4. Revised SPK-9001 empty and full capsid formulation. 5. Revised Table 1 Regimen for Oral Corticosteroids. 6. Added provision to collect safety information between Week 52 and roll-over to long-term follow-up study.	13-Jan-2017
Amendment 5.0 1. This version was never submitted to any Regulatory Authority or any Ethics Committee.	22-Dec-2016
Amendment 4.0 1. Expansion of dose level cohort. 2. Updated laboratory requirements for screening FIX activity level. 3. Updated calculation for vector dose calculation to be based on BMI. 4. Updated Schedule of Activities. 5. Minor administrative changes throughout.	19-May-2016
Amendment 3.0 1. Added non-invasive liver diagnostic tests to Exclusion Criteria #3. 2. Updates to Schedule of Activities. 3. Update to semen collection timepoints. 4. Clarification to reference for empty capsid formulation. 5. Update to Section 8: Study Treatment Management.	03-Mar-2016

DOCUMENT HISTORY

6. Update to clinical assessments and laboratory safety assessments. 7. Update to Appendices A1 and A2. 8. Minor administrative changes throughout.	
Amendment 2.0 1. Clarified incremental recovery, laboratory testing frequency, duration of screening period, unscheduled visit assessments, hemostasis timepoints, additional safety tests, AE reporting responsibilities, duration of safety observation period. 2. Minor administrative changes throughout.	30-Sep-2015
Amendment 1.2 1. Added ECG assessment. 2. Clarified dose escalation. 3. Removed azathioprine from immunosuppressive therapies. 4. Clarified laboratory testing. 5. Added missing information (IND number, some abbreviations. 6. Minor administrative changes throughout	18-May-2015
Amendment 1.1 1. Section 3.2.2 dose level expansion from "≥3% of normal" to "above their baseline". 2. Minor administrative changes throughout.	08-Apr-2015
Original Protocol 1.0	01-Apr-2015

Amendment 7 (14 June 2019)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema CCI [redacted] Section 5.2 Exclusion Criteria	CCI [redacted]	[redacted]

[redacted]

Section # and Name	Description of Change	Brief Rationale
	CCI	CCI
Section 1.1 Synopsis Section 1.3 SoA Section 3 Objectives, Estimands and Endpoints Section 8.7 Genetics Section 10.5 Appendix 5 Genetics	CCI	Banked biospecimens will be collected from participants for exploratory research relating to the drug response in hemophilia B.
CCI	CCI	CCI
• Section 2.3. Benefit/Risk Assessment • Section 4.5. End of Study Definition • Section 5. Study Population • Section 5.1. Inclusion Criteria • Section 5.4. Screen Failures • Section 6. Study Intervention • Section 6.2. Preparation/ Handling/ Storage /Accountability • Section 6.4. Study Intervention Compliance • Section 7.1. Discontinuation of Study Intervention • Section 7.2. Participant Discontinuation / Withdrawal from Study	Template change	The Spark therapeutics protocol amendment document was transferred into the new Pfizer Common Protocol Template (CPT) and mandatory and/or suggested CPT language was adopted in all the sections listed.

Section # and Name	Description of Change	Brief Rationale
• Section 7.3. Lost to Follow up • Section 8. Study Assessments and Procedures • Section 8.2. Safety Assessments and Procedures • Section 8.2.5. Clinical Safety Laboratory Assessments • Section 8.3. Adverse Events and Serious Adverse Events • Section 8.3.1. Time Period and Frequency for Collecting AE and SAE Information • Section 8.3.1.1. Reporting SAEs to Pfizer Safety • Section 8.3.2. Method of Detecting AEs and SAEs • Section 8.3.3. Follow-up of AEs and SAEs • Section 8.3.4. Regulatory Reporting Requirements for SAEs • Section 8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure • Section 8.3.5.1. Exposure During Pregnancy • Section 8.3.5.2. Exposure During Breastfeeding • Section 8.3.5.3. Occupational Exposure • Section 8.3.7. Medication Errors • Section 8.4. Treatment of Overdose • Section 8.7. Genetics • Section 8.8. Biomarkers • Section 9. Statistical Considerations • Section 9.1. Estimands and Statistical Hypothesis • Section 9.1.1. Estimands • Section 9.3. Populations for Analyses • Section 9.4. Statistical Analyses • Section 9.5.1. Data Monitoring Committee (DMC) • Section 10. Supporting Documentation and Operational		

Section # and Name	Description of Change	Brief Rationale
Considerations • Section 10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations • Section 10.1.1. Regulatory and Ethical Considerations • Section 10.1.2. Financial Disclosure • Section 10.1.3. Informed Consent Process • Section 10.1.4. Data Protection • Section 10.1.6. Dissemination of Clinical Study Data • Section 10.1.7. Data Quality Assurance • Section 10.1.8. Source Documents • Section 10.1.9. Study and Site Closure • Section 10.10. Publication Policy • Section 10.1.11. Sponsor's Qualified Medical Personnel • Section 10.2. Appendix 2: Clinical Laboratory Tests • Section 10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting • Section 10.3.1. Definition of AE • Section 10.3.2. Definition of SAE • Section 10.3.3. Recording and Follow-Up of AE and/or SAE • Section 10.3.4. Reporting of SAEs • Section 10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information • Section 10.5. Appendix 5: Genetics • Section 10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments		

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Gene therapy, Open-label, Dose-escalation Study of PF-06838435 (SPK-9001) [adeno-associated viral vector with human factor IX gene] in subjects with hemophilia B.

Rationale

Adeno-associated virus vector (AAV) vectors have been administered in more than 100 gene transfer clinical trials for a wide range of indications, including several studies for hemophilia B, and have demonstrated a good safety profile[1, 2]. Importantly, data from a recent clinical study of AAV8 gene transfer to participants with severe hemophilia B, sponsored by St. Jude Children's Research Hospital – University College London (SJ-UCL), demonstrated that a single peripheral intravenous (IV) infusion of the self-complementary AAV8-LP1-hFIXco resulted in sustained and long-term circulating vector-derived factor IX (FIX:C) activity levels of 2-12%, which were sufficient to improve the bleeding phenotype and reduce the use of regular prophylactic factor IX (FIX) infusions, in some cases completely eliminating them[3]. The previous Sponsor also conducted a study of an AAV8 vector for hemophilia B (AAV8-hFIX19, IND 15149) study was recently conducted. In that trial, the vector was well tolerated and all three dosed participants experienced initial increases in vector-derived FIX:C activity levels. For two of the three participants, expression was short-lived (~2-4 months), likely due to an immune response to some vector component, despite the initiation of an immunosuppressive regimen; for the third participant, expression was longer-lived (~18 months), but trended inexorably downward despite the immunosuppressive therapy. The objective of this study is to evaluate the safety, tolerability, and kinetics of a single IV infusion of PF-06838435 in hemophilia B participants with ≤2 International Units (IU)/dL [≤2%] endogenous factor IX levels.

Dose Rationale

PF-06838435 is an AAV vector designed to drive expression of the human coagulation factor IX (hFIX) transgene and raise circulating levels of endogenous FIX. PF-06838435 is comprised of a bioengineered AAV capsid, AAV-Spark100, and a codon-optimized expression cassette (hFIX39-Padua). AAV-Spark100 is a novel capsid engineered from a naturally occurring AAV serotype, which shows a strong hepatotropic profile in mice and non-human primates (NHPs), comparable to AAV8. The cassette (hFIX39-Padua) encodes the hFIX variant that has higher specific activity than the wild-type (WT) FIX due to the substitution of an arginine for a leucine at amino acid position 338 (R338L). CCI [redacted]

The non-clinical study in NHPs infused with a similar vector, AAV-Spark100-hFIX19-Padua, resulted in therapeutic steady-state vector-derived FIX activity levels without safety concerns. PF-06838435 and AAV-Spark100-hFIX19-Padua share the same regulatory sequences, differing only in choice of codons for codon optimization. Furthermore, studies

in mice and in NHPs have shown that these two vectors yield comparable FIX expression. Thus, the data with AAV-Spark100-hFIX19-Padua in NHPs can be used to predict the vector-derived FIX:C activity levels with PF-06838435 in this study.

An ongoing clinical trial (NCT#01687608) evaluating the safety and efficacy of a self-complementary AAV8 vector encoding the high specific activity hFIX variant, hFIX-Padua (Baxter Healthcare Corporation, BAX-335), is currently being conducted in participants with hemophilia B. Preliminary clinical data of six participants infused at three different dose levels ($2x10^{11}$, $1x10^{12}$, and $3x10^{12}$ vg/kg) achieving vector-derived FIX:C activity levels from <1% to ~60% with no safety concerns were presented at the recent European Association for Haemophilia and Allied Disorders (EAHAD) meeting. Based on Pfizer's knowledge of their results, there have been no thrombotic events observed in the Baxter trial to date. Thus, these data further support the safety of the dose levels being investigated in this study.

This study will investigate up to three dose levels ($5x10^{11}$, $1x10^{12}$, and $2x10^{12}$ vg/kg). Safety of these dose levels is supported by previous human clinical trials of AAV2 and AAV8 vectors encoding hFIX, as well as the NHP studies with AAV-Spark100-hFIX19-Padua and with PF-06838435, in which dose levels up to $5x10^{12}$ vg/kg were infused without evidence of adverse effects. This dose level is ~10-fold higher than the proposed starting clinical dose level of $5x10^{11}$ vg/kg in this study.

Study Design

This is a Phase 1/2a, open-label, non-randomized, uncontrolled, dose-escalation and multi-center study to evaluate the safety, tolerability, and kinetics of a single IV infusion of PF-06838435 in hemophilia B participants with ≤2 IU/dL [≤2%] endogenous factor IX [FIX] levels. Up to 30 evaluable participants will be dosed with a single IV infusion of PF-06838435 at one of three different dose levels.

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

Originally, up to 5 evaluable participants may be dosed in each dose level. An initial dose level may be expanded up to 10 evaluable participants if at least 3 out of 5 participants achieve detectable steady-state vector-derived FIX activity levels above 5%. If, after the above initial dose-level expansion, at least 6 out of 10 participants achieve detectable steady-state vector-derived FIX activity levels above 5%, then further dose-level expansion of up to 10 additional evaluable participants would be allowed (a total of up to twenty evaluable participants at the starting dose level of 5 $x10^{11}$ vg/kg). The administration of PF-06838435 to the first two participants in the starting dose level will be staggered by at least 2 weeks to ensure safety. Additionally, at least eight weeks of safety data from at least 3 out of 5 participants in a given dose level will undergo review by an independent data monitoring

committee (DMC) prior to dosing the first participant in the next dose level. Thus, there will be at least 8 weeks of staggering administration between dose levels.

CCI [redacted]

Objectives, Estimands and Endpoints

As the primary study objective is the assessment of safety and tolerability of a single IV infusion of PF-06838435, the estimands are defined here only for the secondary objective of the study. This study aims to characterize kinetics of PF-06838435 after a single dose administration in the population of participants meeting study's inclusion/exclusion criteria. The vector-derived endogenous (not affected by intercurrent FIX product infusions) FIX:C activity levels will be characterized by post-treatment population mean. The assessment will be done for each dose of PF-06838435. Since only a single IV infusion of PF-06838435 will be administered during the study, there should be no treatment discontinuations. There may be missing data, including those from participants lost to follow-up, but it is anticipated to be rare. The handling of missing data is discussed in the Statistical Analysis Plan (SAP).

Objectives	Endpoints
Primary	
• The primary objective is to evaluate the safety and tolerability of a single IV infusion of PF-06838435 in hemophilia B participants ≥18 years of age with ≤2 IU/dL [≤2 %] endogenous factor IX [FIX]).	Clinically significant changes from baseline in the following: • Physical examination • Vital signs • Laboratory values • Incidence of drug-related adverse events (AEs) (including inhibitor development) • FIX incremental recovery (time at maximum activity [T_{max}] and percent recovery for FIX activity) • Immune response against AAV capsid protein • Immune response against hFIX transgene For those individuals who develop hepatic

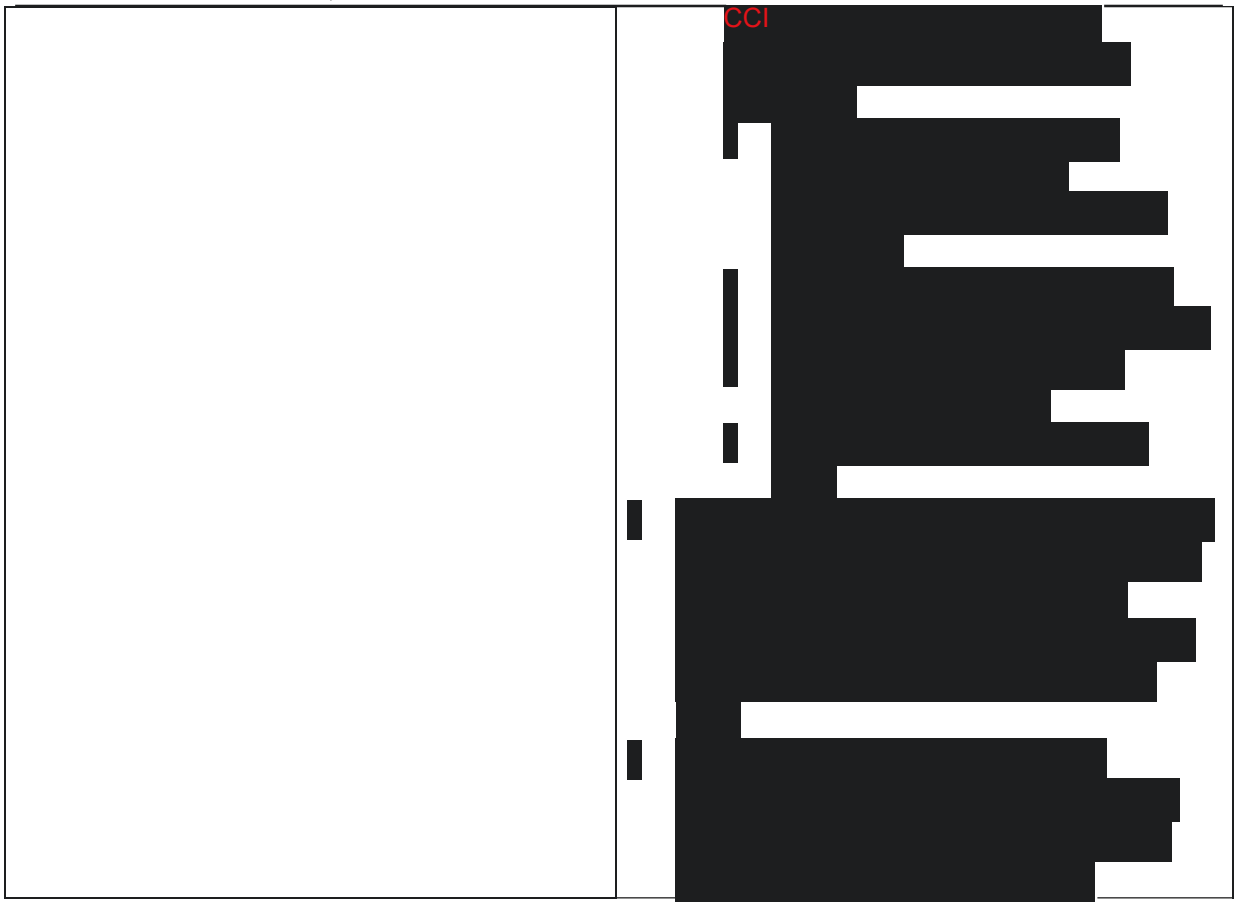
[redacted]

	transaminases (alanine aminotransferase [ALT] and/or aspartate transaminase [AST]) elevation of approximately 1.5-fold or successively increasing during follow-up above baseline (or vector-derived FIX:C activity levels decline without evidence of FIX inhibitor, accompanied by rising interferon [IFN] enzyme-linked immunospot assays [ELISPOTs] on peripheral blood mononuclear cells [PBMCs]) after PF-06838435 infusion, treatment with corticosteroids will be instituted. Alternative immunosuppressive therapies will be considered if the initial corticosteroid treatments are not successful. For any individual who reaches >150% vector-derived FIX:C activity levels after the infusion of PF-06838435, laboratory parameters of thrombotic potential will be assessed.
Secondary	

• The secondary objective is to characterize the kinetics of PF-06838435.	• Vector-derived FIX:C activity levels:
	  • Peak
	  • Steady-state
	• FIX antigen levels

CCI [redacted]	[redacted]

[redacted]



Overall Design

This is a Phase 1/2a, open-label, non-randomized, dose-escalation and multi-center study to evaluate the safety, tolerability, and kinetics of a single IV infusion of PF-06838435 in hemophilia B participants with ≤2IU/dL [≤2%] endogenous factor IX [FIX]). Approximately 20 participants will be dosed with a single IV infusion of PF-06838435 at one of three different dose levels.

Disclosure Statement

This is a single group treatment study with 1 Arm that has no masking.

Number of Participants

Approximately 20 participants will be dosed with a single IV infusion of PF-06838435.

Intervention Groups and Duration

The total duration of the study is approximately 58 weeks, including 6 (±2) weeks of Screening. The study will include the following phases:

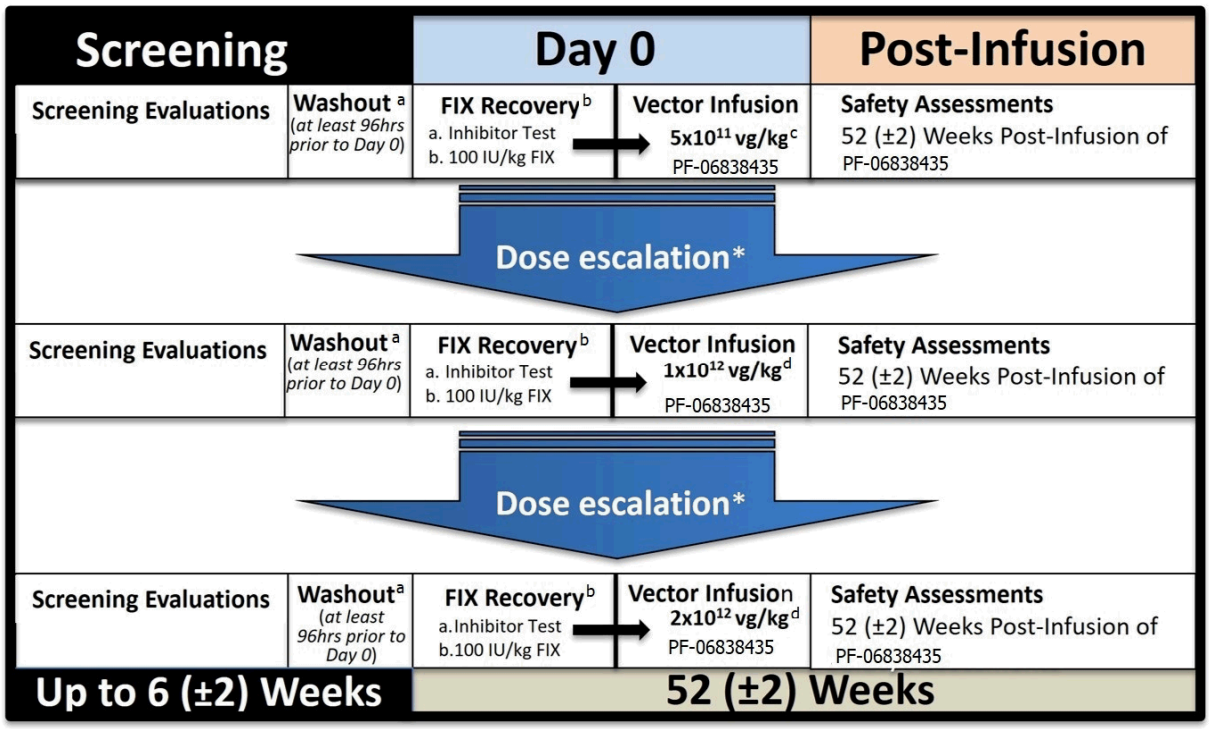
- Screening period [up to 6 (±2) weeks];
- Dosing day – Day 0 [up to 24 hours];
- Safety observation period [52 (±2) weeks].
- Telephone follow-up calls may be conducted by the study staff after the completion of the Week 52 (or End-of-Study) visit until participants have been enrolled into the extension study (for the monitoring of adverse events). Participants who complete 52 (±2) weeks of safety observation (End-of-Study) will be encouraged to enroll in an extension study evaluating the safety, durability, and efficacy of PF-06838435 for an additional 5 years, approximately (a total of 6 years, approximately, when including 1 year from this study).

Data Monitoring Committee: Yes

[redacted]

1.2. Schema

Figure 1. Study Schematic



a. 96 hours (4 days) washout for plasma derived (pd)- or rFIX [or up to 168 hours (7 days) washout for extended half-life rFIX]
b. FIX incremental recovery for FIX products up to 24 (±1) hours after the infusion of the FIX products.
c. First two participants at the starting dose level will be infused at least 2 weeks apart.
d. The first two participants will be infused at least 8 weeks apart. As dose escalation did not occur during the course of this study prior to this amendment (v.7) participants entering the study (low antibody positive) will begin at this dose level. These participants will be dosed at 8-week intervals. If dose escalation occurs, the 8-week interval will remain.

∗ Dose escalation criteria for starting dose $5x10^{11}$ vg/kg group or $1x10^{12}$ vg/kg group are described in Section 4.1.3.2

1.3. Schedule of Activities (SoA)

Tests and Assessments	Week -6 to -1[1]	Day 0[2]		Week 1 - 18 (±2 days)												Week 22 - 52 (±2 weeks)					Unscheduled Visits[3]
	Screening	Pre-Vector Dosing	Vector Dosing	1	2	3	4	5	6	7	8	10	12	14	16	18	22	26	32	42	52 or End-of-Study	
Informed Consent [4]	X																					
Demographics, Medical, Surgical and Hemophilia History (including genotype and HLA) [5]	X																					
Physical Exam, Height, Weight [6], and Vital Signs [7, 8]	X	X [6, 10]	X [6, 8]		X		X		X		X		X		X		X	X	X	X	X [6]	
Liver ultrasound	X [9]																				X	
Target Joint Assessment [10]	X [9]																				X	
Laboratory																						
HBV, HCV, CD4, and HIV Serology Vaccination History [11]	X																					
α-fetoprotein	X																				X	
Standard Safety Panels [12]	X	X			X		X		X		X		X		X		X	X	X	X	X	
Lipid Panel and Urinalysis (dipstick)	X																				X	
LFT and Immunology Tests [13, 14]	X	X		X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X	X	X	X	X	X	X	X	X	X	
Coagulation (aPTT, INR, and TAT) [15]		X																			X	
FIX Activity and Antigen [14]	X	X		X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X	X	X	X	X	X	X	X	X	X	
Bethesda Assay for FIX Inhibitor	X	X					X				X		X		X			X	X	X	X	
AAV Neutralizing Antibody	X	X		X	X		X						X					X			X	

Tests and Assessments	Week -6 to -1[1]	Day 0[2]		Week 1 - 18 (±2 days)												Week 22 - 52 (±2 weeks)					Unscheduled Visits[3]
Genomic Banked Biospecimens Prep-D1	X[29]																				
Global Hemostasis Markers [19]		X																		X	
FIX Product Infusion [17]		X																			
FIX Incremental Recovery [18]		X																			
PF-06838435 Infusion [16,20]			X																		
Review Infusion Log	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Participant's QoL Assessment and Changes in Level of Activity Questionnaires [21]	X [9]						X					X					X			X	
Health-economic Assessment		X					X					X					X			X	
[redacted] C				[redacted]																	
Immunomodulation [23]																					
LFT, Coagulation, Immunology[23]				<<<<< As indicated to monitor immunomodulation optimization (see Section 4.1.5) >>>>>																	
Lipid Panel[23], Urinalysis[23]				<<<<< As indicated to monitor immunomodulation optimization (see Section 4.1.5) >>>>>																	
HCV-RNA Viral Load [23]				<<<<< As indicated to monitor immunomodulation optimization (see Section 4.1.5) >>>>>																	
CD4 / HIV Viral Load [23]				<<<<< As indicated to monitor immunomodulation optimization (see Section 4.1.5) >>>>>																	
Thrombotic Potential Assessment (aPTT, INR, CCI and TAT) [24]				<<<<< As indicated in Section 4.1.6 >>>>>																	
Additional Safety Tests [25]	X																				
Spare Plasma (2mL) [26]	X																				
Serious and non-serious adverse event monitoring [27]	X	<<<<< ongoing >>>>>																			
Concomitant Therapy [28]	X	<<<<< ongoing >>>>>																			

AAV = adeno-associated virus vector; LFT = liver function test; aPTT = activated partial thromboplastin time; FIX = coagulation factor IX; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; RNA = ribonucleic acid; TAT = thrombin-antithrombin; TGA = thrombin generation assay

Notes for Schedule of Activities:

See Appendix 2 for list and description of samples collected including designation for where analysis will occur, local and/or central laboratory for each analyte.

1. The Screening period may be extended up to two weeks for participants who experience a bleed and require infusion(s) with FIX protein products within 96 hours prior to PF-06838435 infusion (Day 0). The reason for extending the screening period must be documented. If the screening period is prolonged greater than 8 weeks, then the participant will need to repeat all screening tests and a new Subject ID will be assigned.
2. At least 96 hours (4 days) washout for regular factor IX products (or up to 168 hours [7 days] washout period for extended half-life factor IX products) on Day 0 prior to infusion is required. The investigational product should NOT be thawed prior to confirmation from the site staff regarding the participant's washout criteria.
3. Unscheduled visits to monitor safety and changes in FIX activity may be necessary during the study. An unscheduled visit may include, but is not limited to, monitoring of hepatic transaminases, FIX transgene expression (FIX activity), FIX antigen (Ag), CPT™ for peripheral blood mononuclear cells (PBMCs) by enzyme-linked immunospot (ELISPOT). A sample for PAXgene RNA may be collected and stored for analysis at the end of study. Any spare plasma from already collected blood samples may also be stored for repeat or additional testing as needed.
4. Informed consent must be obtained from participants prior to any study-related procedures being performed.
5. Demographics include gender, race, date of birth (month and year only), and ethnicity.

Hemophilia history includes (but is not limited to) the date of diagnosis, severity of disease, genotype, HLA, number of exposures to FIX products, type of FIX products received, current dose and infusion regimen of FIX, last dose of FIX received prior to Screening and the first dose of PF-06838435, number of bleeding episodes and factor infusions in the 52 weeks prior to screening, inhibitor history, and allergy/anaphylaxis history.

If genotype and HLA are not known, sample(s) will be drawn for analysis at Screening. Genotype is not a criterion for inclusion or exclusion. However, a documented genotype known to produce a clinically severe phenotype of hemophilia B is required if the participant is otherwise unable to demonstrate severity.

6. Height (cm) is measured at Screening or Day 0 and at End-of-Study visits (Week 52).

Physical Exam is comprehensive (not targeted) and is performed at all clinic visits.

On Day 0 pre-vector infusion, perform physical exam, obtain height (if not available from Screening) and weight; no need to repeat these evaluations post-vector infusion.

Weight (kg) obtained during Screening (the weight obtained from the most recent visit prior to Day 0) will be used to calculate the dose of FIX protein product for FIX incremental recovery and for the dose of PF-06838435.

7. Vital signs include blood pressure (BP), pulse (P), respiratory rate (RR), and oral temperature (°C/°F), and should be taken after the participant has been resting supine or upright for 5 minutes.
8. At Day 0 (for FIX product infusion), obtain vital sign measurements prior to infusion with FIX protein product.

At Day 0 (for PF-06838435 infusion), obtain vital sign measurements at pre-infusion, 30 ± 2 minutes from the start-of-infusion, end-of-infusion ±2 minutes, 3 hours ± 10 minutes, 6 hours ± 10 minutes and 24 (±1) hours from the start-of-infusion of PF-06838435.

9. The assessment needs to be completed between Screening visit and pre-vector infusion.
10. Definition of target joint is described in Section 8.10.3. Assessments include identification of target joints and performance of hemophilia joint health score (HJHS).
11. Screening serology will be performed as follows:

For all participants: hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc), HBV-DNA;

For all participants: HCV-RNA load assay;

For HIV-positive participants: CD4+ count and HIV-1 viral load.

Screening Fibroscan (locally), FibroTest/Fibrosure (Central Laboratory [CL]), or AST-to-Platelet Ratio Index (Local Laboratory [LL] & CL) is required to rule out underlying liver disease in all participants without a known pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy.

12. Laboratory Safety Panels:

Hematology – white blood cell (WBC) count and differential, red blood cell (RBC) count, hemoglobin, hematocrit, CCI and platelet count; ABO blood group at screening only (if not known at Screening)

Clinical Chemistry – sodium (Na), potassium (K), chloride (Cl), phosphate, carbon dioxide (CO2), glucose, blood urea nitrogen [BUN], and serum creatinine

13. LFTs – albumin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH);

Immunology - CPT™ for PBMC by ELISPOT and PAXgene for RNA. PAXgene samples will be stored for analysis at the end of study.

14. Hepatic transaminases and FIX transgene expression will be monitored twice-weekly or thrice-weekly to detect early changes. Between Weeks 1 and 12 post-vector infusion, monitoring will include LFTs, FIX:C, FIX Ag, CPT™ for PBMC by ELISPOT and PAXgene for RNA. Spare plasma, from already collected blood samples will be stored for repeat or additional tests. Some participants may need more frequent monitoring using unscheduled visits.
15. Activated partial thromboplastin time (aPTT) measured in seconds; TAT will be taken just prior to the infusion of FIX product.
16. Participants should be advised to temporarily suspend prophylaxis regimen after vector infusion until being advised by the Investigator to resume.
17. At Day 0, participants should arrive at the clinic with at least 96 hours (4 days) washout of pd-FIX/rFIX or up to 168 hours (7 days) washout of extended half-life FIX product. Participants will receive a single IV infusion of 100 IU/kg of FIX protein product over 10 (±2) minutes.
18. Blood samples will be collected at pre-infusion, 10 (±2) minutes, 1 hour ± 10 minutes, 3 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 (±1) hours from the start-of-infusion of FIX protein product.
19. Thromboelastography (TEG) and/or rotational thromboelastogram (ROTEM) – Only selected participants at selected sites capable of performing these tests locally.
CCI
Blood samples will be collected at pre-infusion and 10 (±2) minutes from the start-of-infusion of FIX protein product on Day 0 and End-of-Study Visits.
20. After the completion of FIX protein product infusion, participants will receive PF-06838435 infused via infusion pump over a period of approximately 60 minutes.
21. Haem-A-QoL, EQ-5D-5L, McGill pain questionnaire, and Hemophilia Activities List (including Changes in Level of Activity) questionnaires will be completed by the participants.
CCI
23. Immunomodulation See Appendix 2: possible tests below:
LFT – albumin, total bilirubin, direct bilirubin, indirect bilirubin, ALP, AST, ALT, total protein, GGT, and LDH;
Coagulation –aPTT, FIX:C, FIX Ag
Immunology - CPT™ for PBMC by ELISPOT and PAXgene for RNA.
Lipid Panel – total cholesterol, HDL (high density lipoprotein), LDL (low density lipoprotein), VLDL (very-low-density lipoprotein), triglycerides,
Serology - HCV-RNA / HCV viral load (if indicated); CD4 / HIV viral load (if indicated);
Urinalysis using dipstick to monitor protein, ketone, pH, specific gravity, and blood.
24. See Appendix 2: possible tests include aPTT, INR, CCI and TAT
25. Additional tests for safety (deemed clinically necessary for evaluation of clinical symptoms or abnormal laboratory findings). For example, ECG for participants >50 years of age.
26. At each blood collection spare plasma (2 mL) from already collected samples will be stored for repeat or additional tests, if needed.
27. Adverse events will be recorded from the time of the start of PF-06838435 infusion through the End-of-Study visit. Any SAE experienced by the participant from the day of signing the ICF through End-of-Study is to be recorded, regardless of the severity of the event or relationship to study treatment.
28. Concomitant medications and procedures with a start date up to 30 days prior to Screening through the End-of-Study visit will be recorded.
29. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

2. INTRODUCTION

PF-06838435 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 endogenous factor IX (FIX:C). The Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products[4] and findings from previous clinical studies with AAV2 and AAV8 vectors were considered in the development of this protocol.

2.1. Study Rationale

Data from a recent clinical study of AAV8 gene transfer to participants with severe hemophilia B, sponsored by SJ-UCL (IND 14031), demonstrated that a single peripheral IV infusion of the scAAV8-LP1-hFIXco resulted in 2-12% sustained and long-term vector-derived FIX:C activity levels which were sufficient to improve the bleeding phenotype and reduce the use of regular prophylactic FIX infusions, in some cases completely eliminating the need for these infusions[3, 5]. A recently conducted clinical study using AAV8-hFIX19 in three participants with hemophilia B (IND 15149) at $1x10^{12}$ and $2x10^{12}$ vg/kg, resulted in vector-derived FIX:C activity levels of up to 16%. Furthermore, preliminary data of a single peripheral IV infusion of self-complementary BAX-335 (scAAV8.hFIX-Padua) at doses of 2 $x10^{11}$ vg/kg, $1x10^{12}$ vg/kg and $3x10^{12}$ vg/kg from the ongoing Baxter study (NCT#01687608) also resulted in detectable vector-derived FIX:C activity levels of <1 to ~60% in six participants[6]. These recent clinical studies demonstrate that AAV vectors are well tolerated.

After a single administration of AAV-Spark100-hFIX19-Padua into NHPs, steady-state hFIX activity levels up to 31%, 68%, and 296% of normal were achieved at $1x10^{12}$, $2x10^{12}$, and $5x10^{12}$ vg/kg dose levels respectively, without safety concerns. PF-06838435 and AAV-Spark100-hFIX19-Padua share the same regulatory sequences and encode identical amino acid sequences. Furthermore, studies in mice and in NHPs have shown that these two vectors yield comparable FIX expression. The objective for this study is to evaluate the safety, tolerability, and kinetics of a single administration of PF-06838435 in participants with hemophilia B.

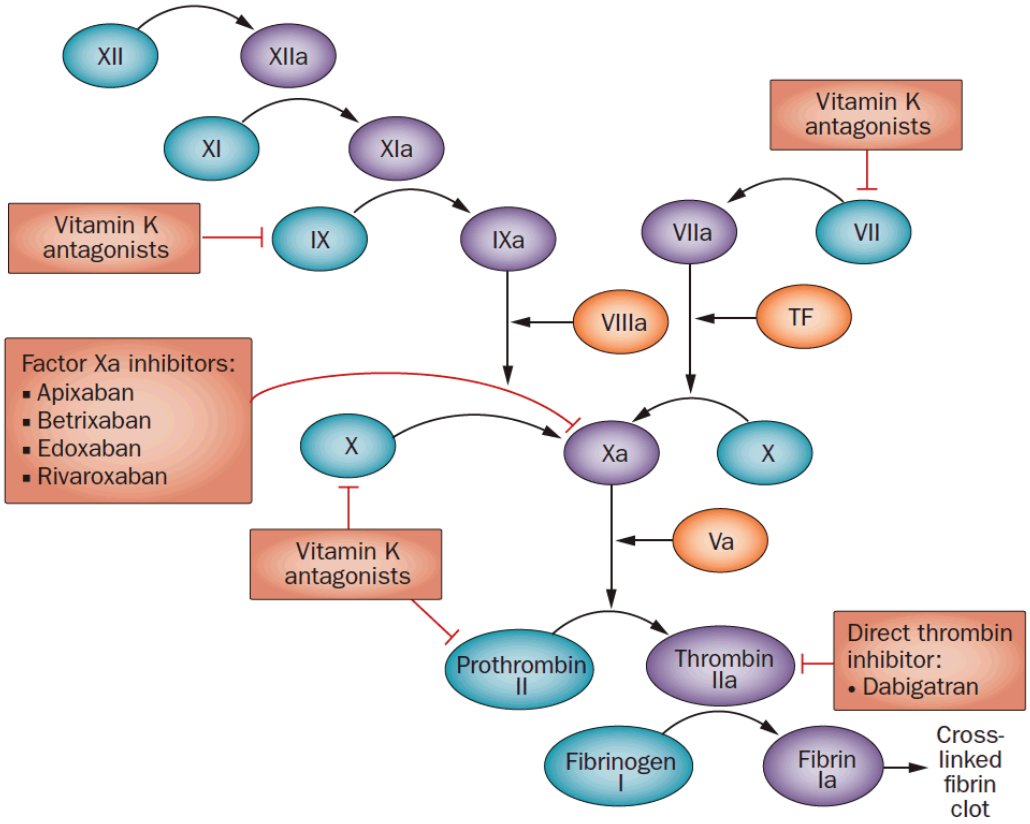
2.2. Background

2.2.1. Hemophilia B

Hemophilia B, or Christmas disease, is a deficiency of blood coagulation factor IX (FIX) and is recessively inherited due to an X-chromosome mutation carried by females and expressed mainly by males, affecting approximately 80,000 people worldwide[7, 8]. A deficiency of FIX results in bleeding into joints, soft tissue, and muscle. Fatal intracranial bleeding is one of the most serious events that can affect individuals with hemophilia B from neonates to the elderly. Bleeding may be associated with trauma or can occur in the absence of trauma (spontaneous bleeding). Depending on the severity of the bleeding event, it can be life-threatening if not treated appropriately. Factor IX, a serine protease, and factor VIII, a cofactor for FIX, work in concert to activate factor X, a central step in the coagulation cascade. The coagulation cascade has two pathways, the Contact Activation Pathway (Intrinsic Pathway) and the Tissue Factor Pathway (Extrinsic Pathway). The plasma factors are activated in the form of a cascade or "waterfall" [9, 10]one after the other until the soluble

plasma protein, fibrinogen, is transformed into a fibrinous clot. The blood coagulation cascade is illustrated in Figure 2.

Figure 2. The Blood Coagulation Cascade[11]



Although platelets are critical to the formation of the hemostatic plug, 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 to 150 IU/dL) of the level in normal pooled plasma. Therefore, clinical features and factor coagulant activity define the severity of the disease.

2.2.2. Clinical Manifestations

About 70% of newborn babies with hemophilia have a positive family history. When the diagnosis is not suspected based on a positive family history, affected children present with bleeding from the umbilical stump, prolonged bleeding after circumcision, bleeding following intramuscular immunization, excessive bruising, or rarely with intracranial hemorrhage. Individuals with hemophilia B (circulating factor IX level ≤2% or less than ≤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 (generally accepted

criterion is a minimum of three bleeds into a single joint within a consecutive three-month period[12]). The inevitable result of such bleeding events is progressive joint damage, leading to disabling arthritis with major effects on physical and psychosocial quality-of-life (QoL) and socio-economic parameters for hemophilia patients. 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[13].

Development of alloantibodies to FIX (ie, inhibitors) is the main complication of any factor replacement therapy[14-16]. Inhibitory antibodies (usually immunoglobulin G subclass 4 [IgG4]) antibodies that neutralize the procoagulant activity of FVIII or FIX) develop in approximately 3-5% of patients with hemophilia B following exposure to factor replacement therapy. This is a lower frequency than is seen in severe hemophilia A. However, hemophilia B inhibitors may present with anaphylactic responses to infusion of factor IX products. In the presence of inhibitory antibodies, replacement of the missing clotting factor by infusion of FIX becomes less effective. Once replacement therapy is ineffective, acute management of bleeding requires agents that bypass FIX activity. Long-term management of inhibitors in hemophilia A typically consists of eradicating the inhibitor through immune tolerance. However, this method is more problematic and less effective in hemophilia B, especially in association with anaphylaxis. Therefore, development of inhibitors significantly adds to patients' disease burden.

2.2.3. Current Therapies for Hemophilia B

There is no available cure for hemophilia B. Factor replacement therapy purified from human plasma first became available more than four decades ago. Although these factor IX products dramatically improved life expectancy and QoL in the USA and Western Europe, they also resulted in exposure of individuals with hemophilia to blood borne viruses – most significantly hepatitis B (HBV), hepatitis C (HCV), and the human immunodeficiency virus (HIV). HIV sero-conversion studies documented that most individuals with hemophilia were infected between 1978 and 1984[17, 18]. In the U.S.A., most patients with severe hemophilia who were born before 1987 are HIV positive, and many have already died from complications related to the acquired immune deficiency syndrome (AIDS). HCV disease can cause chronic and progressive hepatitis, with eventual development of cirrhosis, and affects the majority of persons with hemophilia B born before 1987. Late complications of HCV are an increasing cause of death in adults who have been infected for decades[19,7]. In the 1990's, concerns of viral contamination[20] precipitated the development of high-purity virus-inactivated plasma-derived products and genetically engineered recombinant factors with no animal- or human-plasma-derived proteins to minimize the risk of disease transmission[21, 22]. However, these products have not circumvented all of the problems of protein-based therapies[23, 24].

Current treatment of the disease is based on venipuncture and IV administration of either plasma-derived or recombinant FIX protein replacement home therapy to raise the circulating FIX (FIX:C) activity level to the lowest effective dose to achieve either resolution of bleeding (on-demand treatment) or prevention of bleeding[8, 25, 26] (prophylaxis treatment). Venous access via peripheral veins remains the preferred option for the administration of FIX

products[27] because it allows a large amount of product to be administered frequently as a short infusion using small needles (23-25 gauge). The frequency of administration of FIX products varies among individuals and is tailored to the individual's clinical status, taking into consideration the type of bleed, frequency of bleeding, and goal of treatment for the participant. Both U.S. National Hemophilia Foundation and the World Federation of Hemophilia[8] established recommendations of plasma factor levels and duration of administration for different types of bleeds based on observations over the years. Improvements in FIX replacement therapy have vastly increased the QoL and life expectancy of individuals with hemophilia B; a recently licensed modified FIX agent with extended half-life[28] provided more convenient dosing options[29]. Prophylactic therapy for hemophilia has gradually increased among the adult population in the U.S.A. but is still not universally practiced for several reasons. The expense is prohibitive (an average adult individual with severe hemophilia who elects on-demand treatment to resolve bleeding events spends $100,000 on factor replacement therapy each year; prophylaxis treatment may triple the yearly cost). Furthermore, children lacking suitable peripheral veins may require central venous access devices (CVADs) for factor infusion, which may result in catheter-related infections and local thrombotic complications[30] that greatly affect the durability of the device for the patient[31]. Reported rates of catheter-related infection due to the residual blood left at the infusion site in hemophilia vary widely; a meta-analysis calculated a pooled incidence of infection of 0.66 per 1000 CVAD days[31] (CI: 0.44-0.97 per 1000 CVAD days). Extended half-life FIX protein products that require less frequent infusions may potentially decrease problems related to venous access[32, 33].

Gene therapy has been the goal for curative treatment of hemophilia since the initial cloning of the genes more than 30 years ago. As a proposed alternative approach, gene therapy may potentially reduce short-term disability and long-term hemophilic arthropathy, reduce incidence of central nervous system (CNS) bleeding, eliminate the need for indwelling IV catheters or frequent factor infusion, and improve participants' overall QoL and functional independence[34]. Indeed, this prediction has been borne out in the recent SJ-UCL clinical trial, in which all 10 participants who received gene transfer have reduced their use of prophylactic factor products. Additionally, at least 5 of these participants have reduced factor consumption by greater than 90% while remaining free of spontaneous bleeding episodes[3, 5].

Several features make hemophilia B a good model for gene therapy. The first advantage of hemophilia B as a model for gene therapy is that precise regulation of transgene expression is not required. Therapeutic range is remarkably wide, from >1% to 150% of normal. It is clear, based on data from administration of FIX products into patients with hemophilia B, that levels above ≤150% are not associated with ill-effects since the protein circulates as a zymogen (inactive precursor). Second, as stated, >1% circulating FIX activity levels may provide protection against chronic arthropathy and CNS bleeding. Patients with levels of >5% have mild severity and only rarely experience spontaneous bleeding episodes (although they exhibit abnormal bleeding in response to hemostatic challenges such as surgery or trauma). A third advantage of hemophilia B is the availability of large and small animal models of the human disease. Clearly, animal models are major assets in efforts to establish an experimental basis for gene therapy. In the case of hemophilia, there are well characterized, naturally occurring canine models of the disease and genetically engineered hemophilic mice [35, 36,37,38, 39]. Finally, it should be noted that determination of therapeutic

efficacy is straightforward and unequivocal in the case of hemophilia B since plasma levels of FIX are easy to measure and correlate well with clinical disease severity.

2.3. Benefit/Risk Assessment

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

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

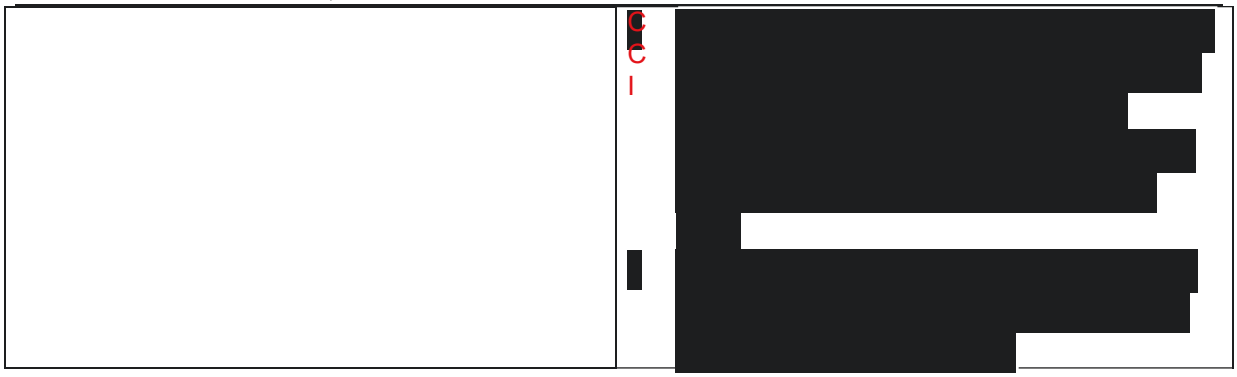
Objectives	Endpoints
Primary	
• The primary objective is to evaluate the safety and tolerability of a single IV infusion of PF-06838435 in hemophilia B participants ≥18 years of age with ≤2 IU/dL [≤2 %] endogenous factor IX [FIX]).	Clinically significant changes from baseline in the following: • Physical examination • Vital signs • Laboratory values • Incidence of drug-related adverse events (including inhibitor development) • FIX incremental recovery (time at maximum activity [T_{max}] and percent recovery for FIX activity) • Immune response against AAV capsid protein • Immune response against hFIX transgene For those individuals who develop hepatic transaminases (ALT and/or AST) elevation of approximately 1.5-fold or successively increasing during follow-up above baseline (or vector-derived FIX:C activity levels decline without evidence of FIX inhibitor, accompanied by rising IFN ELISPOTs on PBMCs) after PF-06838435 infusion, treatment with corticosteroids will be instituted. Alternative immunosuppressive

	therapies will be considered if the initial corticosteroid treatments are not successful. For any individual who reaches >150% vector-derived FIX:C activity levels after the infusion of PF-06838435, laboratory parameters of thrombotic potential will be assessed.
Secondary	

• The secondary objective is to characterize the kinetics of PF-06838435.	• Vector-derived FIX:C activity levels:
	  • Peak
	  • Steady-state
	• FIX antigen levels

CCI [redacted]	[redacted]

[redacted]



As the primary study objective is the assessment of safety and tolerability of a single IV infusion of PF-06838435, the estimands are defined here only for the secondary objective of the study. This study aims to characterize kinetics of PF-06838435 after a single dose administration in the population of participants meeting study's inclusion/exclusion criteria. The vector-derived endogenous (not affected by intercurrent FIX product infusions) FIX:C activity levels will be characterized by post-treatment population mean. The assessment will be done for each dose of PF-06838435. Since only a single IV infusion of PF-06838435 will be administered during the study, there should be no treatment discontinuations. There may be missing data, including those from participants lost to follow-up, but it is anticipated to be rare. The handling of missing data is discussed in the Statistical Analysis Plan (SAP).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1/2a, open-label, non-randomized, dose-escalation and multi-center study to evaluate the safety, tolerability, and kinetics of a single IV infusion of PF-06838435 in hemophilia B participants with ≤2IU/dL [≤2%] endogenous factor IX [FIX]). Approximately 20 evaluable participants will be dosed with a single IV infusion of PF-06838435 at one of three different dose levels, see Schema in Section 1.2.

4.1.1. Initial Sequence of Enrollment

The following two staggering strategies are employed in this study based on the recommendation from The Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products[4]:

1. The first two participants at the starting dose level ($5x10^{11}$ vg/kg) will be infused with PF-06838435 at least 2 weeks apart; and

2. There will be at least 8 weeks of staggering between each dose level. At least 8 weeks of safety data from at least 3 out of 5 participants in a given dose level will undergo review by an independent DMC prior to dosing the first subject in the next dose level.

A schematic of the study design is presented as Figure 1 Section 1.2

CCI [redacted]

4.1.3. Dose Escalation and Expansion

4.1.3.1. Initial Dose Escalation

Dose escalation and dose level expansion strategies are employed in the study based on vector-derived FIX activity levels as well as any immune responses against AAV capsid. There will be no dose escalation if at least 3 participants in any dose level achieve steady-state vector-derived FIX activity levels of ≥40%. Steady-state levels are based on 2 separate vector-derived FIX:C activity level measurements (at least two weeks apart) starting from Week 8-12 with adequate washout (ie, 96 hours for factor IX plasma-derived [pd]- or r-FIX and up to 168 hours for extended half-life recombinant factor IX (rFIX) from FIX product.

Dose escalation will occur under the following scenarios:

1. If neither of the first two participants in a given dose level achieve detectable steady-state vector-derived FIX activity levels above their baseline, then escalation to the next dose level will occur, provided there are no safety concerns; or

2. If less than 3 evaluable dosed participants in a given dose level achieve steady-state vector-derived FIX activity levels between 3% to 40% of normal, then escalation to the next dose level will occur, provided there are no safety concerns.

At least 8 weeks of safety data from at least 3 out of 5 participants in a given dose level will undergo review by the independent DMC prior to infusing the first participant in the next dose level (See Section 4.1.1 for staggering strategy). The decision to dose escalate will require the agreement of Pfizer and DMC.

Dose level expansion will occur for the following scenarios:

1. If at least one of the first two participants at the low or middle dose level achieve steady-state vector-derived FIX activity level above their baseline, then up to an initial 5 evaluable participants will be dosed at the respective dose.

2. If one or both of the first two participants in any dose level achieve circulating vector-derived FIX activity levels above their baseline (without using any FIX product) but with a decline to their baseline levels due to an immune response to vector capsid that is NOT well-managed by corticosteroids, then dose escalation will not occur, and instead up to a total of 5 evaluable participants will be dosed at the respective dose.

3. If at least 3 out of 5 participants in the given dose level [scenario "1" above] achieve steady-state vector-derived FIX activity levels above 5%, then the initial dose level may be expanded up to 10 evaluable participants.

4. If at least 6 out of 10 participants in the given dose level [scenario "3" above] achieve steady-state vector-derived FIX activity levels above 5% after the initial dose-level expansion, then the initial dose level may be further expanded by up to 10 additional participants (a total of 20 evaluable participants would be allowed).

CCI

4.1.4. FIX Incremental Recovery

FIX incremental recovery will be measured up to 24 (±1) hours post-infusion of FIX protein products to assess time at maximum activity and percent recovery for exogenous FIX activity. The exogenous FIX activity levels will be determined by one-stage clotting assay. Participants are required to have at least 96 hours of washout for pd- or r-FIX or up to approximately 168 hours of washout for extended half-life rFIX prior to FIX incremental recovery test on Dosing Day (Day 0).

FIX incremental recovery assessments will be conducted by collecting blood samples at various time-points up to 24 (±1) hours from the start of FIX protein product infusion. Blood samples on Day 0 will be collected pre-infusion, 10 (±2) minutes, 1 hour ± 10 minutes, 3 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 (±1) hours from the start-of-infusion of FIX protein product.

Samples for thrombin generation assessments will also be collected on Day 0 at pre-infusion and 10 (±2) minutes from the start-of-infusion of FIX protein infusion and evaluated by an

CCI performed at the central laboratory. For participants at selected sites depending on the testing capabilities, additional samples for global hemostasis may also be collected at pre-infusion and 10 (±2) minutes from the start-of-infusion of FIX protein infusion and evaluated by the whole blood TEG and/or rotational thromboelastogram (ROTEM) locally.

4.1.5. Immunomodulation Optimization (ONLY for Participants Who Develop Hepatitis Transaminitis)

Based on observation and experience from earlier clinical studies of liver-directed AAV gene transfer, including the SJ-UCL trial[3, 5], earlier clinical studies sponsored by Spark Therapeutics', who was also the initial Sponsor of this study, and the Baxter trial (NCT#01687608), participants may develop an apparent immune response to the vector capsid participants, as evidenced by a transient rise in transaminases (AST and/or 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.

A tapering course of oral corticosteroids 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 (CTL). The mechanism for this immune reactivity is not clear, but viruses may be causal.

Based on guidelines published by the American Association for the Study of Liver Diseases (AASLD) [41, 42] and in the absence of alternative etiology, and from the study data of the SJ-UCL group, treatment for vector-induced hepatitis would be instituted if:

1. In the absence of alternative causes, a transaminase value is approximately 1.5-fold above baseline (Day 0) OR is successively increasing during follow-up (at the Investigator's discretion, they may choose to wait for a repeat transaminase value which remains elevated, or is further increased, or they may choose to initiate treatment); or

2. Vector-derived FIX:C activity levels decline without evidence of inhibitor, corticosteroids may be added at the discretion of the Investigator.

Oral corticosteroids (such as prednisolone/prednisone) will be used per the AASLD guidelines, with modification allowed by the Investigator and agreed by the medical monitor based on response to laboratory parameters and/or participant tolerance of the regimen:

Table 1. Recommended Initial Regimen for Oral Corticosteroids

Schedule	Prednisolone/Prednisone (mg/day)
Week 1	~100 - 60
Week 2	60[a]
Week 3	40

Table 1. Recommended Initial Regimen for Oral Corticosteroids

Schedule	Prednisolone/Prednisone (mg/day)
Week 4	30
Week 5	30
Week 6	20[b]
Week 7	15
Week 8	10

a. Please see paragraph below.
b. Maintain at 20 mg/day until transaminases (and ELISPOT) 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.

Approximately 100-60 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, 60 mg/PO QD [a] 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 begun to decline or have returned to approximately baseline (pre-administration) levels. See Table 1 above.

The following schedule of combined oral corticosteroids and IV 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	Prednisolone/Prednisone (mg/day)	Methylprednisolone (g/day)
Day 1-3	n/a	1
Day 4-7	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

There is extensive experience with corticosteroids and immunosuppressive regimens in hemophilia: first, as a maneuver to eradicate antibodies to factor VIII or IX, clinically termed inhibitors[43-45] and second, in the setting of liver transplantation due to the high prevalence of hepatitis C among adults with hemophilia[46, 47]. Many individuals with hemophilia have been maintained on standard liver transplant immunosuppression regimens for years.

Corticosteroids have been used to treat people with asthma, idiopathic thrombocytopenic purpura, and other medical conditions for years. For participants with severe hemophilia B, the benefit of long-term expression of a modest level of clotting factor far outweighs the risk of a course of immunomodulatory drugs.

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 utilize 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 disappearance from the peripheral blood of capsid-specific T cells. While on immunomodulatory regimens, participants will also be monitored for side effects, including 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 immune hepatitis develops in any participant, following investigational product administration and if 2 or more participants are non-responsive to immunomodulatory regimens, or if the value of the transaminases continue to rise, consideration of more intensive immunomodulatory regimens will be entertained per recommendation from the independent Data DMC. Regimen recommendations will require agreement from the DMC, Sponsor Medical Monitor, and the Investigator.

4.1.6. 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 and the and the now closed Baxter study using hFIX-Padua, 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 on Day 0 (prior to FIX protein product infusion) will be used to establish baseline value.

4.1.7. Duration of Study Participation

The study will consist of the following phases:

1. Screening period (up to 6 [±2] weeks);

2. Dosing day (Day 0);

3. Safety observation period (52 [±2] weeks post-infusion of PF-06838435).

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

4.1.7.1. Screening Period

Potential participants will undergo the screening assessments described in the Schedule of Activities up to 6 (±2) weeks prior to the infusion of PF-06838435 once the consent process is completed at the vector-administration center. If the screening result of FIX:C activity level is >2% due to recent infusion of factor IX protein product, then the severity of hemophilia B may be confirmed by documented historical evidence from a certified laboratory demonstrating the FIX:C activity level ≤2% or from a documented genotype known to produce a clinically severe phenotype of hemophilia B. If FIX:C activity is not ≤2% at screening or documented historical evidence is not available and genotype are not known, sample(s) will be drawn for analysis at Screening. Genotype is not a criterion for inclusion or exclusion. However, a documented genotype known to produce a clinically severe phenotype of hemophilia B is required if the participant is otherwise unable to demonstrate severity. Once the eligibility is verified, participants are required to undergo a washout of FIX protein products for at least 96 hours (4 days) prior to the Dosing Day (Day 0) to establish baseline value of FIX:C and FIX inhibitor. The screening period may be extended up to 2 weeks for participants who have a bleeding event requiring FIX protein product infusion within 96 hours prior to Day 0 (Dosing Day). If screening is prolonged greater than 8 weeks, then the FIX inhibitor, anti-AAV-Spark100 capsid antibody, biochemistry, hematology, vital signs, and physical examination screening assessments must be repeated to ensure continued eligibility. The reason for prolongation of screening should be clearly documented.

Screening assessments would also be done to verify participant eligibility are described in Section 8.10.1.

4.1.7.2. Dosing Day

Assessments and procedures to be performed on Dosing Day (Day 0) are described in the Schedule of Activities. Participants will receive a bolus infusion of FIX protein product in about 10 minutes for FIX incremental recovery (Section 6.1.1) followed by a single IV infusion of PF-06838435 at the vector-administration center. The complete dose of PF-06838435 will be infused via infusion pump over a period of approximately 60 minutes under medical supervision. Vital signs will be taken at various time-points up to approximately 24 hours from the start of infusion (see Schedule of Activities).

Blood samples for FIX incremental recovery will be collected pre-infusion of the FIX protein product, 10 (±2) minutes [end-of-infusion], 1 hour ± 10 minutes, 3 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 (±1) hours from the start-of-infusion. Samples for thrombin generation assessments will also be collected pre-infusion and 10 (±2) minutes from the start-of-infusion of FIX protein infusion and evaluated by an CCI [redacted] performed at the central laboratory. For participants at selected sites, depending on the testing capabilities, additional samples for global hemostasis such as whole blood TEG and/or ROTEM may also be collected pre-infusion and 10 (±2) minutes from the start-of-infusion of FIX protein infusion and evaluated locally.

4.1.7.3. Post-Infusion

Participants will report to either the vector-administration center or follow-up center for safety evaluations, according to the protocol assessments (See the Schedule of Activities for further details regarding each visit), for up to 52 (±2) weeks after infusion of PF-06838435. During the safety observation period, in-home service provider can be utilized, if needed, for mobile-phlebotomy and sample-collection services during the visits which do not require a physical examination.

4.2. Scientific Rationale for Study Design

This study will investigate up to three PF-06838435 dose levels ($5x10^{11}$, $1x10^{12}$, and $2x10^{12}$ vg/kg). Safety of these dose levels is supported by previous human clinical trials of AAV2 and AAV8 vectors encoding hFIX, as well as the NHP studies with AAV-Spark100-hFIX19-Padua and with SPK-9001, in which dose levels up to $5x10^{12}$ vg/kg were infused without evidence of adverse effects.

Dose escalation and dose level expansion strategies are employed in the study based on vector-derived FIX activity levels as well as any immune responses against AAV capsid.

The primary study objective is the assessment of safety and tolerability of a single IV infusion of PF-06838435. This study also aims to characterize kinetics of PF-06838435. The vector-derived endogenous (not affected by intercurrent FIX product infusions) FIX:C activity levels will be characterized by post-treatment population mean. The assessment will be done for each dose of PF-06838435.

As no formal hypotheses will be tested in this study, the sample size is based on the need to establish the initial safety and kinetic profile of PF-06838435. Up to 20 evaluable participants will be dosed in the study (Section 9.3).

4.3. Justification for Dose

Non-clinical pharmacology, toxicology, and biodistribution studies of AAV-Spark100-hFIX19-Padua have been performed in three animal models (wild-type [WT] mice, HB mice, and NHPs) to evaluate expression and safety. PF-06838435 has also been infused into NHP and demonstrated to drive expression of FIX at levels equivalent to AAV-Spark100-hFIX19-Padua. Long-term safety and immunogenicity of the FIX-Padua protein were evaluated in a hemophilic canine model using an AAV8-FIX-Padua vector. These data are relevant to PF-06838435 since FIX gene delivery using AAV-Spark100 results in similar levels of expression as compared to gene delivery using AAV8 in these species. Based on the Sponsor's experience, studies in mice have not been predictive of FIX expression levels in humans, but studies in dogs and NHPs have correlated well with levels in human participants. The non-clinical studies in NHP using AAV Spark100-hFIX19-Padua infused at a dose of 1x1012 vg/kg resulted in steady-state vector-derived FIX activity levels of ~27% (range 22.7 30.7%).

A dose of $5x10^{12}$ vg/kg was administered without evidence of adverse effects in NHPs. It is widely accepted that maintaining factor activity levels above 1-2% of normal may prevent bleeding and ultimately arthropathy in patients with severe hemophilia[48, 49]. Based on large

animal models of the disease and prior clinical experience with AAV8-hFIX19, the starting dose of $5x10^{11}$ vg/kg may result in detectable circulating vector-derived factor IX (FIX:C) activity levels above background levels. This starting clinical dose ($5x10^{11}$ vg/kg) is ~10 fold lower than the highest dose studied in the Good Laboratory Practice (GLP) toxicology study. Furthermore, non-clinical safety data demonstrate that doses of $1x10^{12}$ vg/kg, $2x10^{12}$ vg/kg and $5x10^{12}$ vg/kg are generally well tolerated in NHPs and support the proposed up to three dose levels of $5x10^{11}$, $1x10^{12}$, and $2x10^{12}$ vg/kg to be investigated in this study.

It is worth noting that the preliminary data of an ongoing Baxter trial (NCT#01687608) using self-complementary AAV8-hFIX-Padua (BAX-335), presented at the 8th Annual Congress of the EAHAD on 12th February 2015 in Helsinki, Finland, showed vector-derived FIX:C activity levels of ranging from <1 – 60% at doses of 2 $x10^{11}$ vg/kg, $1x10^{2}$ vg/kg and $3x10^{2}$ vg/kg with no safety concerns[6]. One common aspect of our previous trial (IND 9398) and Baxter's study is that vector preparations with minimal empty capsid content were used[50, 51]. The outcome of both trials in the low dose levels was disappointing, showing sub-therapeutic or no FIX expression in most of the participants. Specifically, three out of three participants treated with $4x10^{11}$ vg/kg of AAV2-hFIX16 and one out of two participants treated with $2x10^{11}$ vg/kg of BAX-335 manifested no detectable factor IX expression. Activity levels from the second participant dosed with BAX-335 could only be detected due to the hyperactivity of the Padua variant as antigen levels may not have been higher than 0.25 - 0.5% of normal.

Meanwhile, both participants infused with $2x10^{11}$vg/kg of scAAV2/8-LP-hFIXco with an empty:full capsid ratio of approximately 5:1[52] in the SJ-UCL hemophilia B trial expressed FIX above background levels[5]. Thus, the Sponsor hypothesizes the presence of an excess of empty capsids may absorb low-level NAbs and non-NAbs, permitting liver transduction after peripheral vector infusion even at low doses[53]. PF-06838435 will contain a mixture of empty and full capsid particles (cp), at a ratio comparable to the ratio used in the SJ-UCL study.

Additional information for the C0371005 Phase 1/Phase 2a study results may be found in the Investigator's Brochure (IB).

4.3.1. Study Stopping Rules

Pfizer may terminate this study at any time after informing the Investigators. Pfizer, or designee, will notify the Investigator(s) and appropriate regulatory authorities if the study is

suspended, terminated or completed. If the study is suspended or terminated, the following instructions should be followed, unless the DMC and/or the Study Medical Monitor advise otherwise:

1. Participants who have already received PF-06838435 will continue to maintain the protocol schedule of activities;

2. Participants who have already enrolled into the study but have not received PF-06838435 will wait for DMC recommendation. The scheduled date for PF-06838435 infusion may be postponed or cancelled.

The occurrence of any of the following medically important events will result in suspension of further enrollment while the events are under investigation:

- Any drug-related death during the study;

- Any participant develops drug-related or possibly drug-related Grade III-IV toxicity such as FIX inhibitor, allergic reaction (bronchospasm and anaphylaxis), excluding elevated transaminases;

- Any participant develops drug-related or possibly drug-related Grade III-IV elevated transaminases that fails to improve or resolve within four weeks on the immunosuppressive regimens;

- Any participant develops drug-related or possibly drug-related Grade IV (>10-fold) elevated transaminases;

- Any participant reaches >150% of normal vector-derived FIX:C activity levels and develops drug-related or possibly drug-related thrombotic event after vector infusion (with the exception of IV infusion-site thrombophlebitis) or if any participant develops a sustained (defined as > 6 weeks) FIX activity levels of >150%;

- Participant experience a medically important event that warrants further evaluation;

- Any occurrence of a malignancy at any point after vector infusion that is possibly, probably, or definitely related to the investigational product.

It is important to note that AAV vector-mediated insertional mutagenesis, if it should occur, is not likely to be observed in the first year after gene transfer; therefore, Pfizer intends to provide long-term safety monitoring of participants in the extension study.

In addition to halting enrollment, such an event will be handled as a serious adverse event (SAE) and reported in the time frame according to Section 8.3.1.1 (Reporting of SAEs to Pfizer) of the protocol. The DMC will review data relevant to the event and will receive input from Pfizer and/or Investigator before providing appropriate recommendations. The event and the DMC's recommendation will be discussed with the U.S. Food and Drug Administration (FDA) and other regulatory authorities prior to re-initiation of enrollment.

All participants who were infused with the investigational product will continue to comply with the follow-up schedule according to the protocol.

4.4. End of Study Definition

A participant is considered to have completed the study if he has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

If a decision is made to terminate the study, the Investigators will be notified. No additional participants will be enrolled or dosed and the appropriate end-of-study assessments will be performed for all participants enrolled in the study at that time.

At the time of last subject last visit (LSLV), final assessment results and laboratory tests are generally not available, thereby necessitating the need for follow-up action. Sponsor studies involve specialized tests, which have to be sent to specialized centers; these data then have to be reconciled with the rest of the data. Thus, clinical sites are still active post-LSLV and may only be closed following database lock, when all required participant information has been confirmed as both received and clean, including follow-up information for any SAEs/reactions.

4.5. Extension Study (C0371003)

Participants who complete study assessments at the defined end of study will be encouraged to enroll in C0371003 evaluating the long-term safety, durability, and efficacy of PF-06838435. A 5-year long-term follow-up (LTFU) is planned based on the November 2006 FDA Guidance entitled Gene Therapy Clinical Trials – Observing Participants for Delayed Adverse Events[54]. The Investigator should discuss the extension plan with the participants prior to enrolling them in this study and again at the End-of-Study (Week 52) visit. Any AEs, safety events or unscheduled visits between Week 52 (or End-of-Study) of this study and the first study visit of the extension study will be captured in the source data for the subject and entered into the extension study database after the subject has agreed and completed the informed consent process.

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:

Age

1. Participant must be male and ≥18 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Have hemophilia B with ≤2 IU/dL (≤2%) endogenous FIX activity levels as documented from a certified clinical laboratory at the time of screening. If the screening result is >2% due to insufficient washout from the FIX product, then the severity of hemophilia B may be confirmed by documented historical evidence from a certified clinical laboratory demonstrating ≤2% FIX coagulant activity (FIX:C) or from a documented genotype known to produce clinically severe phenotype of hemophilia B;

3. Have had ≥50 prior exposure days (EDs) to any recombinant and/or plasma-derived FIX protein products based on historical data from participant's records/history;

4. a) Prophylaxis participants: Have had bleeding events and/or infusion with FIX products during the last 12 weeks, as documented in the participants' medical records; or

   1. b) On-demand participants: Have had ≥4 bleeding events in the last 52 weeks and/ or chronic hemophilic arthropathy (pain joint destruction and loss of range of motion) in one or more joints;

5. Have no history of hypersensitivity or anaphylaxis associated with any FIX or IV immunoglobulin administration;

6. Have no measurable FIX inhibitor as assessed by the central laboratory; or documented no prior history of FIX inhibitor after 50 EDs (family history of inhibitors will not exclude the participant) and no clinical signs or symptoms of decreased response to FIX administration;

7. Have acceptable laboratory values sampled at screening and reviewed prior to Day 0:

   - Hemoglobin ≥11 g/dL;
   - Platelets ≥100,000 cells/μL;
   - AST, ALT, alkaline phosphatase ≤2x upper limit of normal (ULN);
   - Bilirubin ≤3x ULN (Bilirubin levels above the laboratory's normal range are acceptable in individuals with a documented history or laboratory evidence of Gilbert's Disease);
   - Creatinine ≤2.0 mg/dL.

Sex

8. 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 during the intervention period and 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

9. 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

5.2. Exclusion Criteria

Unless otherwise specified, participants who meet any of the following criteria at screening or prior to dosing of PF-06838435 (Day 0) are not eligible for the study. See Section 8.10 for additional study assessments:

1. Hepatitis B screening (acute and chronic):
    - A participant who has either Hepatitis B surface antigen (HBsAg) assessment which is positive, or HBV-DNA is positive/detectable.
    - A participant who is currently undergoing anti-viral therapy for hepatitis B.
2. Hepatitis C screening (acute or chronic):
    - A participant who is currently undergoing anti-viral therapy for chronic hepatitis C
    - A participant is not eligible if his HCV-RNA load assay result is positive/detectable.

3. Significant underlying liver disease.

    - A participant is not eligible if any of the following pre-existing diagnoses, which are indicative of significant underlying liver disease, are present in the medical record:

        - Portal hypertension, or;
        - Splenomegaly; or
        - Hepatic encephalopathy.

    - All participants who do not have the listed pre-existing diagnoses in (1) must have the following assessments performed at Screening:

        - A participant is not eligible if the serum albumin level is below the testing laboratory's lower limit of normal; and
        - At least one of the following diagnostic tests for liver fibrosis indicates ≥ stage 3. The following results are indicative of fibrosis ≥ stage 3 and exclude the participant from participation:

            - FibroScan, with a score >8.3 kPa units
            - FibroTest/FibroSURE with a result >0.48; or
            - AST-to-Platelet Ratio Index (APRI) >1.

4. Have serological evidence of HIV-1 or HIV-2 with CD4 counts ≤200/mm^3. Participants who are HIV-positive and stable, have an adequate CD4 count (>200/mm^3) and undetectable viral load (<50 gc/mL) documented in prior medical records and at Screening, and are on an antiretroviral drug regimen are eligible to enroll;

5. Participants receiving 5x10^{11} vg/kg with anti-AAV-Spark100 neutralizing antibody titers ≥1:5; [redacted]

6. Have history of chronic infection or other chronic disease that the Investigators consider to constitute an unacceptable risk;

7. Have been dosed in a previous gene therapy research trial within the last 52 weeks or enrolled in a clinical study with an investigational drug within the last 12 weeks

8. Any concurrent clinically significant major disease, or other unspecified reasons that, in the opinion of the Investigator, and/or Sponsor makes the participant unsuitable for participation in the study; and

9. Unable or unwilling to comply with the schedule of visits and study assessments described in the clinical protocol.

[redacted]

5.3. Lifestyle Considerations

Participants are expected to remain compliant with inclusion criterion 8 at least until 3 consecutive ejaculate samples test negative for vector shedding.

One subject was noted to have increased liver function tests (LFTs) in the setting of excessive alcohol consumption in the long term follow up period. Upon discontinuation of alcohol, 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 alcohol consumption during the study. Participants who report increased alcohol consumption should have at a minimum 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 SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened in consultation and with the agreement of the medical monitor.

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

Refer to investigational product (IP) manual for specifics on the preparation, storage, handling, disposal, and accountability of investigational product.

ARM Name	PF-06838435/Fidanacogene elaparvovec
Intervention Name	PF-06838435/Fidanacogene elaparvovec
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 dose calculation
Dosage	5×10^{11} vg/kg single administration 1×10^{12} vg/kg single administration 2×10^{12} vg/kg single administration For participants with body mass index (BMI) exceeding 30 kg/m^2, the study dose will be calculated based on an adjusted body weight

	determination that assumes a maximum permissible BMI of 30 kg/m^2. For example, a subject who is 6'2" and weighs 370 pounds (BMI 47.5 kg/m^2) would receive a vector dose based on an adjusted body weight of 234 pounds (which is the body weight associated with a BMI of 30 kg/m^2 for a 6'2" individual).
Route of Administration	Intravenous infusion/injection
IMP and NIMP	IMP (investigational medicinal product)
Sourcing	Provided centrally by the Pfizer
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 Names	PF-06838435, SPK-9001, AAV Spark100 hFIX39-Padua, Adeno associated viral vector with human factor IX Padua gene.

6.1.1. Dose Schedule and Administration

Refer to Figure 1 for the Study Schematic and Study Specifics (Section 4.1.1) for a description of the sequence of enrollment. Following the bolus infusion of the participant's usual FIX protein product in about 10 minutes for FIX incremental recovery, the participant will be infused with PF-06838435 IV for approximately 60 minutes via infusion pump. The rate of administration should be determined based on the total volume of the PF-06838435 required for the participant to infuse for approximately 60 minutes.

6.1.2. FIX Incremental Recovery of FIX Products

Participants should be reminded to have washout of at least 96 hours (4 days) without FIX protein product, or longer washout for extended half-life FIX protein product, prior to any blood draw and infusion on Day 0. On Day 0 participants will be infused with 100 IU/kg of their usual FIX protein product over 10 (±2) minutes, under the supervision from the site staff and/or Investigator(s) to assess FIX incremental recovery. Number of vials, total volume, and total dosage are monitored and recorded by the site staff.

6.2. Preparation/Handling/Storage/Accountability

The investigational product must be stored in a secure location. Accountability for the study drug is the responsibility of the Investigator. More details concerning this responsibility are included in the IP Manual. The Investigator or his/her designee is responsible for the proper dispensing of the investigational product. The IP is to be dispensed only to participants who are enrolled and eligible based on the inclusion and exclusion criteria in this study. IP vials are for one time use only; any IP remaining in the vial after infusion should not be used for another subject.

Study site staff and investigational pharmacy personnel should refer to the Pharmacy Brochure for specific instructions on the handling, preparation, administration, and disposal of the investigational product.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
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 IP Manual and it should be reviewed carefully. Once eligibility has been confirmed, the IP can be ordered noting that will take at least 3 weeks for product delivery

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Screening of Participants

Participants must provide consent before any screening tests or assessments are performed. At the time of consent, the participant will be enrolled into the study. Participating study sites are required to document all screened candidates initially considered for inclusion in this study. If a participant is excluded from the study, the reasons for exclusion will be documented in the participant's source documents and on the screening log.

Participants may have screening laboratory results repeated once if the initial test falls outside of the protocol criteria. At the second screening, the participant will be assigned a different participant identification number.

For participants whose genotype is not known, a sample will be drawn for analysis at screening. This is not an inclusion or exclusion criterion; the participant's refusal to have this genotype sample taken would not exclude the participant from the study unless the severity of the disease is unable to be verified due to inadequate washout.

Genotyping may provide information regarding the predisposition of genotypic subpopulations to experience different bleeding frequencies. The development of an inhibitor to treatment with factor concentrates is the single most serious complication of factor replacement. One of the decisive risk factors for the development of inhibitors is the type of mutation (eg, deletion or missense) that codes for a protein that may be absent, truncated, or present, but not functional. There is a correlation between the resultant protein and the likelihood of developing inhibitors to factor replacement[55].

6.3.2. Enrollment of Participants

Each participant will be assigned a unique participant identification number after the informed consent process is completed. No participant may be dosed prior to obtaining the unique participant identification number. The Investigator must confirm and verify the eligibility per criteria in Section 5.1 and Section 5.2 (following the review of screening results from the certified clinical laboratory and other documents). Participant identification numbers that are assigned will not be reused even if the participant does not receive investigational product or fails screening.

6.3.3. Randomization

Not applicable. This is a non-randomized study.

6.3.4. Blinding Procedures

Not applicable. This is an open-label study.

6.4. Study Intervention Compliance

Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

Compliance with the infusion of FIX protein product and PF-06838435 on Day 0 is to be monitored and recorded by site staff.

After the infusion of FIX protein product on Day 0, participants will immediately be infused with PF-06838435. PF-06838435 will be infused via infusion pump and will be supervised by the investigational staff. The vial lot number, total volume, and infusion time are monitored and recorded by the site staff. Therefore, full compliance with PF-06838435 infusion is anticipated.

6.5. Concomitant Therapy

The use of concomitant therapies or procedures, as defined below, must be recorded on the participant's eCRF, according to instructions for eCRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

A concomitant therapy is any drug or substance administered between participant consent (at Screening) and last study visit. Participants taking medication routinely for a pre-existing condition should be on a regimen, which has been stable for at least 3 weeks, and dosage changes should not be anticipated during the post-infusion period for this study. All concurrent prescription and non-prescription medications, including over-the-counter and alternative preparations (including herbal remedies, vitamins, and health food supplements), should be recorded at baseline and throughout the study period.

Medication use in the 30 days prior to screening, as well as the use of concomitant therapies or procedures must be recorded on the participant's eCRF, according to instructions for

eCRF completion. AEs related to administration of these therapies or procedures must be documented on the appropriate eCRF.

6.5.1. Allowed Therapy

During the study participants are requested to temporarily suspend their prophylaxis regimen, but participants may take:

- FIX product, as needed. Usage of clotting factors (product, date, dosage, reason) will be recorded in the infusion log.

Participant should be instructed to discuss any new medications, including non-prescription drugs and herbal preparations, with the Investigator prior to taking them.

Other therapies considered necessary for the participant's welfare may be given at the discretion of the Investigator. All such therapies must be recorded in the eCRF.

6.5.2. Disallowed Therapy

The following concomitant medications are not permitted during the study:

1. Blood products such as red blood cells (RBC), platelets, and fresh frozen plasma, except as required during a surgery.

2. Non-steroidal anti-inflammatory drugs that are known to inhibit platelet function, for example naproxen, aspirin, ibuprofen.

3. Acetylsalicylic acid (aspirin) or ibuprofen; however, other non-steroidal anti-inflammatory drugs are permitted.

4. Participants who are participating in other investigational therapies and concomitantly used with PF-06838435.

5. Any other therapies under investigation and concomitantly used with the investigational product (participants are not allowed to participate concurrently in another clinical study).

6.5.3. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (eg, surgery/biopsy, physical therapy) or diagnostic assessment (eg, blood gas measurement, bacterial cultures) performed between the time the participant is enrolled (at screening) and last study visit. Concomitant procedures must be recorded in the eCRF

6.6. Dose Modification

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

The dose of 1×10^{12} and 2×10^{12} 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 the Schedule of Activities (SoA) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. All assessments outlined for Week 52 visit should be completed. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any remaining samples but data already generated from the samples will continue to be available, and may be used to, to protect the integrity of existing analyses. The investigator must document any such requests in the site study records.

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

If a participant withdraws from the study after enrollment, but before receiving a dose of the investigational product (PF-06838435), then follow-up beyond the screening evaluations is not required. Withdrawn participants without receiving a dose of the investigational product will be replaced.

7.3. Lost to Follow up

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

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

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

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.
- Immediate safety concerns should be discussed with Pfizer immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

No formal efficacy evaluations will be performed. However, the following information will be collected for exploratory efficacy evaluations:

- Vector-derived FIX:C activity levels (including peak and steady-state levels)
- FIX antigen level

- Annualized bleed rate (ABR) (spontaneous and traumatic)
- Annualized factor IX consumption
- Health-economic parameters (Section 8.9)
- Number of target joints (Section 8.10.3)
- Health-related quality-of-life (Section 8.10.4)
- Changes in level of activity (Section 8.10.5)

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examination including height and weight.

8.2.2. Vital Signs

Vital sign measurements including blood pressure, pulse rate, respiratory rate, and temperature (°C/°F), and should be taken after the subject has been resting supine or upright for 5 minutes.

8.2.3. Electrocardiograms

Electrocardiograms (ECG) for participants >50 years of age or if clinically indicated.

8.2.4. Clinical Safety Assessments

- Hemophilia medical history for the 26 weeks preceding screening.
- Target joint history for the 52 weeks preceding screening. Target joints will be identified and assessed during this study. A target joint is defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, ankle) into which repeated bleeding occurs (frequency of 3 or more bleeding episodes into the same joint in a consecutive 12 week period) and with symptoms of pre-existing target joint involvement (eg, synovitis, persistent swelling, effusion, limitation of range of motion) (Ota et al. 2007).
- Assessment for adverse signs and symptoms (AE and SAE recording) and concomitant medications
- Concomitant therapy and procedures

8.2.5. Clinical Safety 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 or within 52 ± 2 weeks after the last dose of study intervention 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.

8.3. Adverse Events and Serious Adverse Events

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

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 (Section 7.2)

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

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 last study visit.

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

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

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

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 Pfizer within 24 hours of it being available.

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

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

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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 Appendix 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 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.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

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

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

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

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

8.3.6. 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 (Section 10.3) 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.

• 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.

8.3.7. 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 participating participant.

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, Pfizer should be notified immediately.

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

An overdose is any dose more than the intended dose of investigational product given to a participant. Overdoses are not considered AEs; however, all overdoses should be recorded on an SAE form and faxed to Pfizer Safety within 24 hours. An overdose should be reported even if it does not result in an AE. Overdoses do not need to be recorded as AEs but any symptoms of an overdose should be reported in the eCRF as AEs; dosing information is recorded on an eCRF.

For this study, any dose of PF-06838435 greater than the intended dose of 1 x 10^{12} vg/kg or 2 x 10^{12} 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 Medical Monitor immediately.
- 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 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 will be analyzed at a certified clinical laboratory by one-stage assay. Results will be used to determine peak, and steady-state vector-derived circulating FIX activity levels.

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9. STATISTICAL CONSIDERATIONS

The details of statistical methodology are specified in the Statistical Analysis Plan (SAP). In general, statistical analyses will be primarily descriptive in nature. Summary statistics will be presented for all safety, PK and efficacy endpoints (including vector-derived FIX:C activity levels over time after PF-06838435 administration, annualized bleeding rate, etc.).

No formal statistical hypothesis testing will be performed. Various exploratory statistical tests may be applied to data generated from this study to generate hypotheses to be tested in subsequent trials.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

As the primary study objective is the assessment of safety and tolerability of a single IV infusion of PF-06838435; the estimands are defined here only for the secondary objective of the study. This study aims to characterize kinetics of PF-06838435 after a single dose administration in the population of participants meeting study's inclusion/exclusion criteria. The vector-derived endogenous (not affected by intercurrent FIX product infusions) FIX:C activity levels will be characterized by post-treatment population mean. The assessment will be done for each dose of PF-06838435. Since only a single IV infusion of PF-06838435 will be administered during the study, there should be no treatment discontinuations. There may be missing data, including those from participants lost to follow-up, but it is anticipated to be rare. The handling of missing data is discussed in SAP.

9.1.2. Statistical Hypotheses

No formal hypotheses will be tested in this study.

9.2. Sample Size Determination

No formal hypotheses will be tested in this study. The sample size is based on the need to establish the initial safety and kinetic profile of PF-06838435 and select dose for the proper efficacy assessment. Approximately 20 participants will be dosed in the study.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF.
Dosed	All participants who were enrolled and received a single intravenous infusion of PF-06838435.
Evaluable	All dosed participants.
Safety	All dosed participants.

Defined sets for analysis	Description
Safety Analysis Set	All dosed participants.
Pharmacokinetics Analysis Set	All dosed participants who have collected vector-derived factor IX in circulation (FIX:C) activity levels enabling acceptable determination of the peak and steady-state derived activity level.
CCI [redacted]	[redacted]

Defined sets for analysis	Description
FIX Incremental Recovery Analysis Set	All dosed participants who have received 100 IU/kg of FIX protein product infusion and have completed the blood sample collection 30 (±2) min post infusion for FIX protein product enabling determination of FIX incremental recovery.

9.4. Statistical Analysis

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	No primary efficacy endpoints.
Secondary	• Vector-derived steady state FIX activity level will be analyzed in PK analysis set by dose level. • Vector-derived peak FIX activity level will be analyzed in PK analysis set by dose level. • FIX antigen levels will be analyzed in PK analysis set by dose level.
CCI	[redacted]

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Descriptive analyses of drug-related adverse events, laboratory abnormalities, immune response to AAV capsid protein, etc. will be conducted.
Secondary	No secondary safety endpoints.
CCI	[redacted]

9.4.3. Other Analyses

Other analyses will be described in the statistical analysis plan finalized before database lock.

9.5. Interim Analyses

No formal interim analyses are planned.

9.5.1. Data Monitoring Committee (DMC)

This study will use a data monitoring committee (DMC). The DMC is independent of the study team and includes external members. The DMC charter describes the role of the DMC 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 International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations, including applicable privacy laws.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 (Code of Federal Regulations), 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.
- 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 Pfizer with sufficient, accurate financial information as requested to allow Pfizer 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/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- 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 or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by Pfizer in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the 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.
- Participants who are rescreened are required to sign a new ICF.

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

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

- Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

- To protect the rights and freedoms of natural persons with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (eg, Protected Health Information Authorization in North America).

The participant will not be identified by name in the eCRF or in any study reports and these reports will be used for research purposes only. Pfizer, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the participant's personal medical data confidential.

10.1.5. Committees Structure

10.1.5.1. Independent Data Monitoring Committee

The independent DMC is composed of independent experts in hemophilia or immunology. The independent DMC will be responsible for reviewing the safety data and other data (as needed) on a regular basis during the course of the study. The specifics regarding the DMC organization and procedures will be outlined in the DMC Charter.

10.1.5.2. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Regulatory Authorities and ethics committees must be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with necessary timelines.

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 patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (clinical study report [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 patient 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. Patient 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 for a minimum of 15 years after study completion unless local regulations or institutional policies require a longer 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.
- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.
- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Study Monitoring Plan.

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 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 Pfizer 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 or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the central laboratory (CL) and/or by the local laboratory (LL).
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3. Protocol-Required Laboratory Assessments

Assessment	Description

Hematology (CL)	• WBC count with Differential:
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
	• RBC count
	• Hemoglobin
	• Hematocrit
	• Platelet count

Clinical Chemistry (CL)	• Sodium • Potassium • Chloride • Bicarbonate • Glucose • Phosphate • Serum creatinine • BUN
Lipid Panel (CL)	• LDL • VLDL • HDL • Triglycerides • Total Cholesterol
ABO (LL)	• ABO group
Urinalysis (CL)	• pH • Specific Gravity • Protein • Blood • Ketones • Glucose
Liver Function Tests (LL and CL)	• Albumin, • Total bilirubin • Direct bilirubin • Indirect bilirubin • ALP • AST • ALT • Total protein • GGT • LDH
Liver Fibrosis (CL)	• FibroTest/Fibrosure (if applicable)
Coagulation (LL, CL as noted)	• FIX activity, aPTT (LL and CL) • FIX antigen, INR, TAT, CCI (CL) • ROTEM and/or TEG (LL where available) • FIX inhibitor (Nijmegen Bethesda), (LL screening visit only, CL screening and all other visits)
AAV Neutralizing Antibody (CL)	• PF-06838435 Neutralizing Antibody
Immunology (CL)	• ELISPOT IFN-γ with PBMCs to assess cellular immune responses to AAV capsid and to FIX
CCI [redacted]	[redacted]

Table 3. Protocol-Required Laboratory Assessments

Assessment	Description
	• Urine • Semen
Hepatitis B and Hepatitis C (CL)	• Hepatitis B Surface Antigen • Total Hepatitis B Core Antibodies • HBV DNA • Hepatitis C Virus Antibodies • HCV RNA
α-Fetoprotein (CL)	• Pre-existing liver disease
HIV Serology (CL)	• HIV-1/HIV-2 Antibody Screen
HIV Viral load and CD4 (CL)	• HIV-1 Qualitative, RNA
Spare Plasma (CL)	• Aliquoted from already collected blood samples
PAXgene (CL)	• RNA extraction and transcriptomic assays
Day 1 Banked Biospecimen (CL)	• Pharmacogenomics

AAV = adeno-associated virus vector; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = ; AST = aspartate transaminase; BUN = blood urea nitrogen; CL = Central laboratory; ELISPOT = enzyme-linked immunospot assay; FIX = coagulation factor IX; GGT = gamma-glutamyl transferase; HBV DNA = hepatitis B deoxyribonucleic acid; HCV RNA = hepatitis C virus ribonucleic acid; HDL = high density lipoprotein; HIV = human immunodeficiency virus; IFN-γ = interferon gamma; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = Low-density lipoprotein; LL = Local laboratory; PBMC = peripheral blood mononuclear cells; RBC = red blood cells; ROTEM = rotational thromboelastogram; TAT = thrombin-antithrombin; TEG = thromboelastography; TGA = thrombin generation assay; VLDL = very-low-density lipoprotein; WBC = white blood cells

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 Meeting 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.
- 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. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

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

or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

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

In this study, the following events are considered medically important and must be reported as SAEs:

- Any drug-related death during the study;
- Any subject develops drug-related or possibly drug-related Grade III-IV toxicity such as FIX inhibitor, allergic reaction (bronchospasm and anaphylaxis), excluding elevated transaminases (Section 10.8);
- Any subject develops drug-related or possibly drug-related Grade III-IV elevated hepatic transaminases that fails to improve or resolve within four weeks on the immunosuppressive regimens (Section 10.8);
- Any subject develops drug-related or possibly drug-related Grade IV (>10-fold) elevated transaminases (Section 10.8);
- Any subject reaches >150% of normal vector-derived FIX:C activity levels and develops drug-related or possibly drug-related thrombotic event (with the exception of IV infusion-site thrombophlebitis) or if any subject develops a sustained (defined as > 6 weeks) FIX activity levels of > 150%;
- Any occurrence of a malignancy at any point after vector infusion that is possibly, probably, or definitely related to the investigational product.

Participants will be informed of early symptoms and signs of thrombotic phenomena, including pain and/or tenderness along a vein, swelling of an arm or leg without pain or tenderness, redness along a vein, low fever without any known reason (such as a cold or flu), sudden shortness of breath or difficulty breathing or coughing, sudden chest pain, sudden severe headache or changes in vision, and numbness or tingling in arms or legs. If such an event occurs while the subject is at home, the subject will be instructed to seek immediate medical care.

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 SAEs 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 or breastfeeding, 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

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure	**None**	All (And exposure during pregnancy [EDP] supplemental form for EDP)

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Life-threatening: Occurrence of the event places the subject at immediate risk of death.
- Death: Occurrence of the event results in the death of the subject.

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.
If applicable, the toxicity grade in Appendix 8 should also be noted.

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

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the investigational product:

Relationship	Description
Not related	An event that does not follow a reasonable temporal sequence from administration of investigational product *AND* that is likely to have been produced independently by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

Unlikely	Any event that does not follow a reasonable temporal sequence from administration of investigational product *OR* that is likely to have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
Possibly	Any reaction that follows a reasonable temporal sequence from administration of investigational product *OR* that follows a known response pattern to the suspected drug *AND* that could not be reasonably explained by the known characteristics of the subject's clinical state, toxic or environmental factors or other modes of therapy administered to the subject.
Related	Any reaction that follows a reasonable temporal sequence from administration of investigational product *AND* that follows a known response pattern to the suspected drug *AND* that recurs with re-challenge, *AND/OR* is improved by stopping the drug or reducing the dose.

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 Safety 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 Pfizer Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

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

taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Pfizer Safety by telephone.
- Contacts for SAE reporting can be found in the ISF.

SAE Reporting to Pfizer Safety via Paper CRF

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

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

Contraception Guidance:

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

Collection of Pregnancy Information:
For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done

irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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

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

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

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

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis.
- Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class, treatments for the disease(s) under study or the disease(s) themselves.
- 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 (Section 8.7) will not be stored beyond the completion of this study (eg, Clinical Study Report finalization).
    - Samples for banking (see Section 8.7) will be stored indefinitely or other period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked Biospecimens will be labelled with a code.
- The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

[redacted]

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 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 major histocompatibility complex (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.

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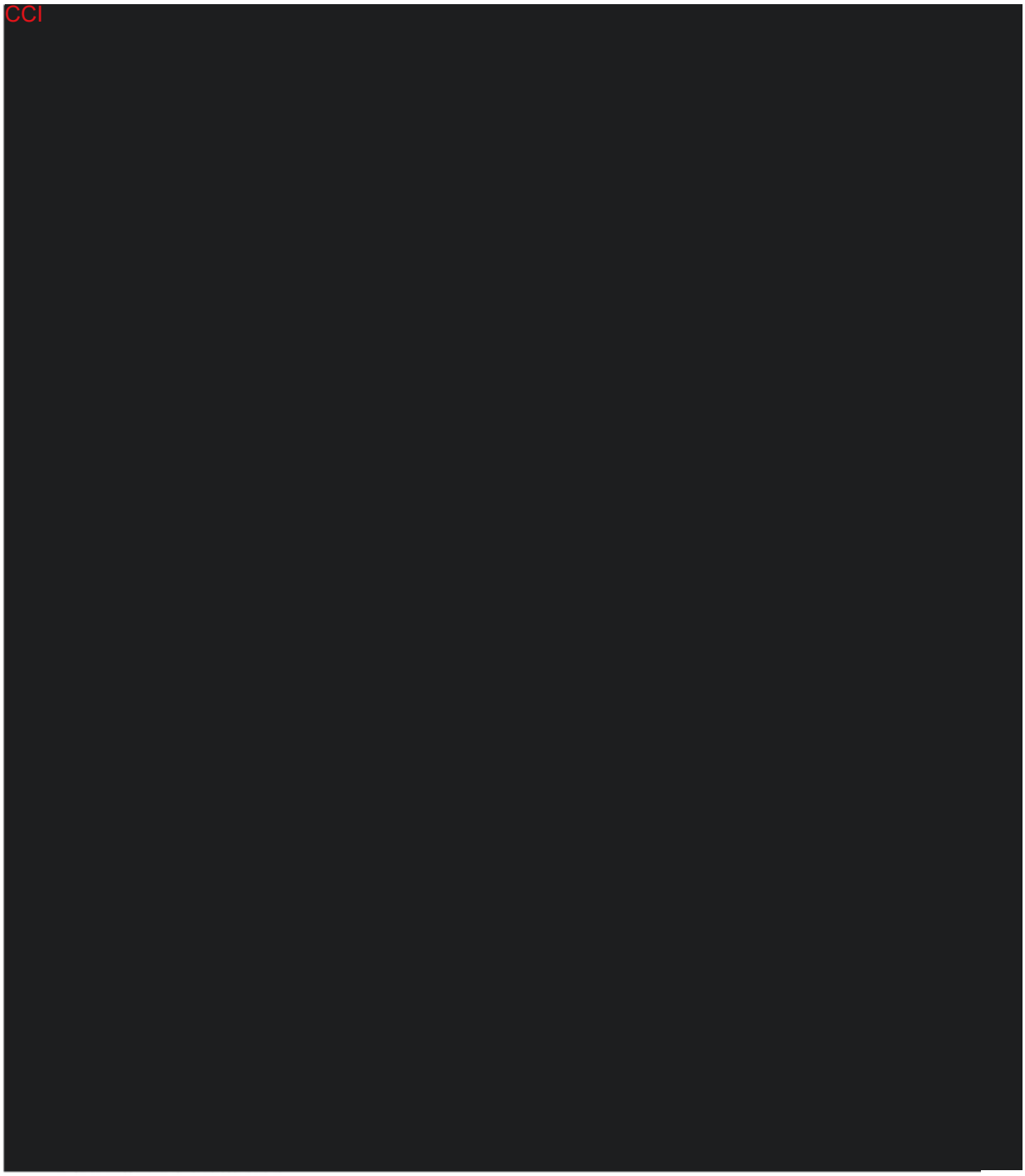
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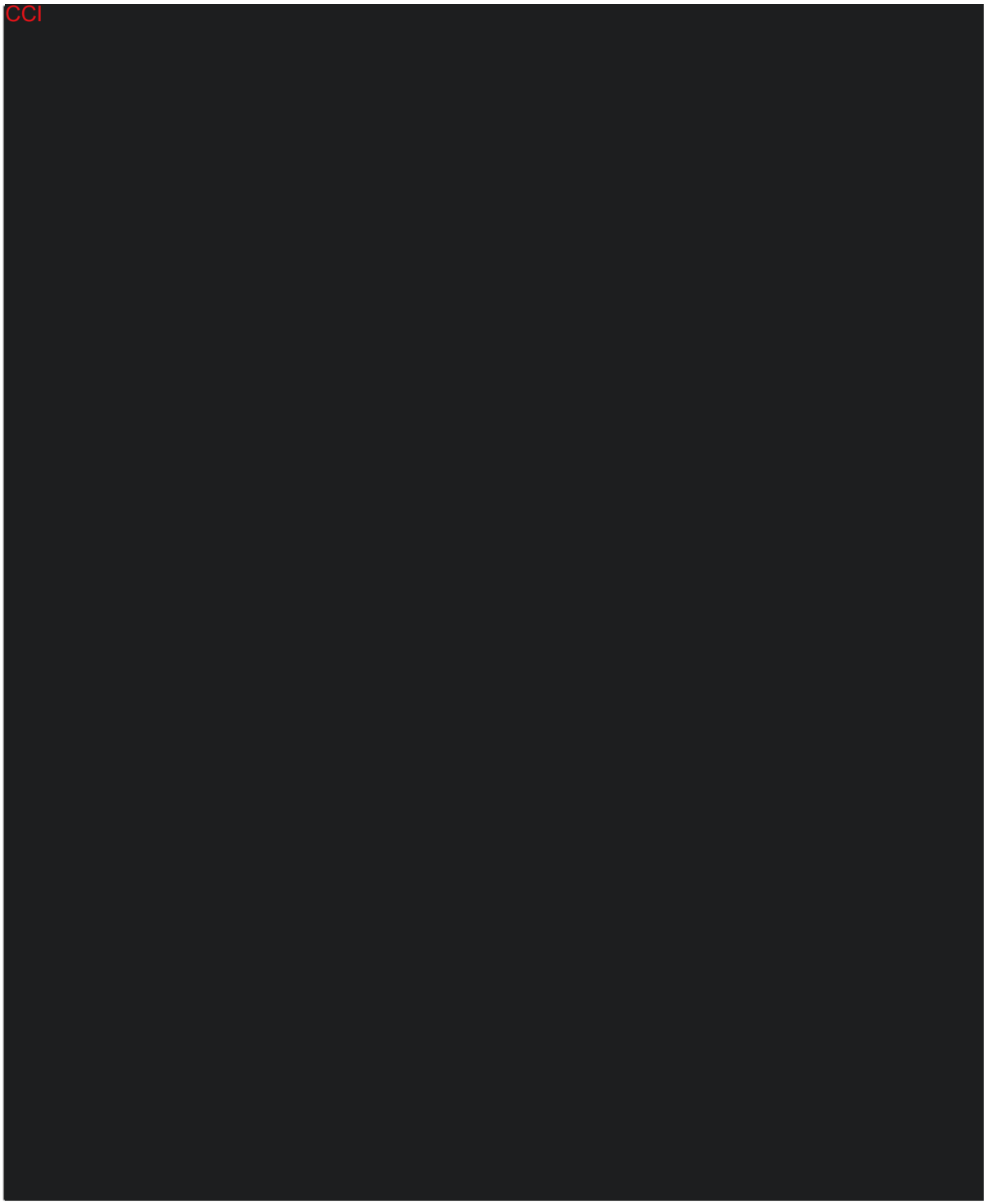
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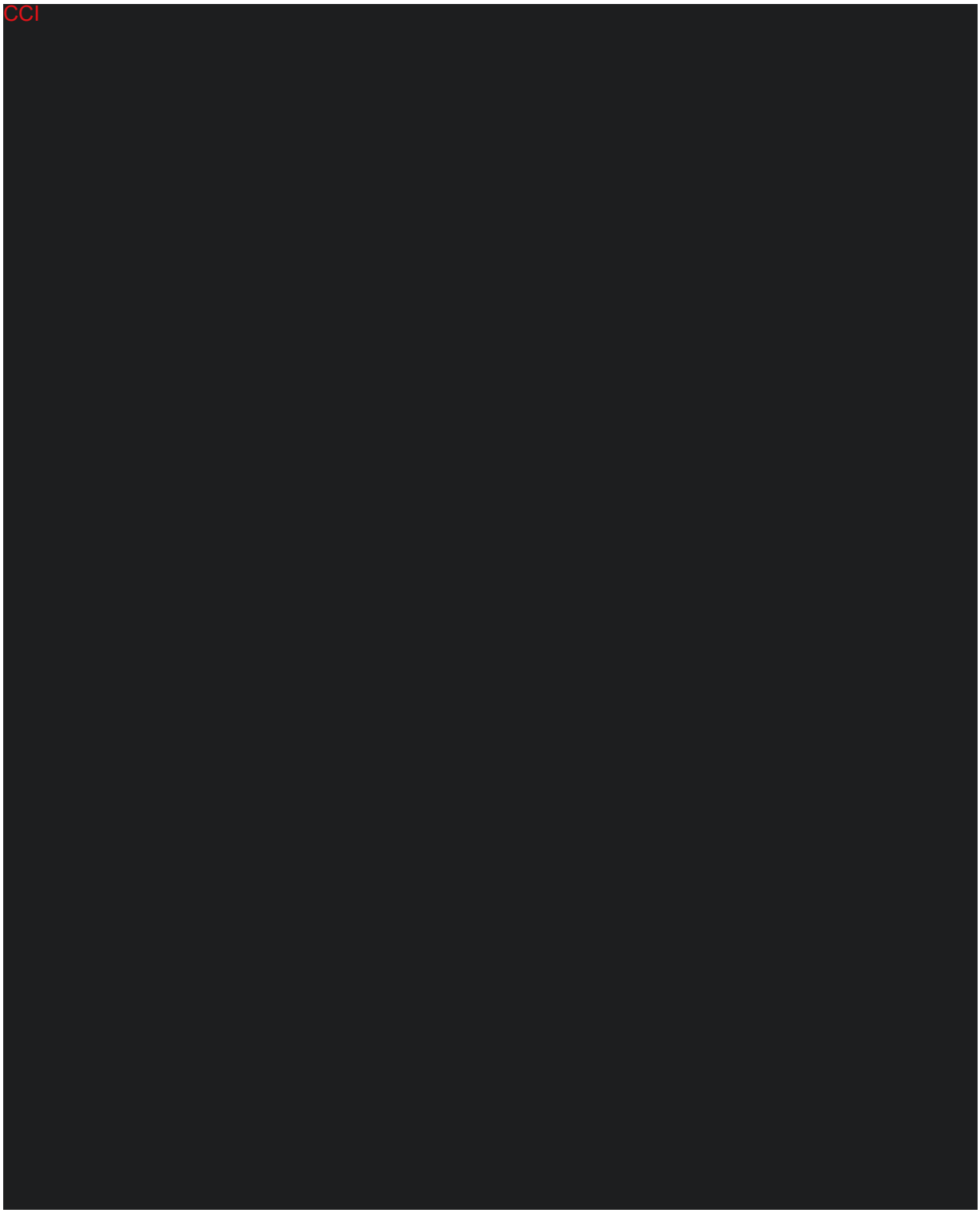

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10.8. Appendix 8: Toxicity Scale

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
General				
Fever	37.8–38.5°C	38.6–39.5°C	39.6–40.0°C	>40.0°C
Chills	Mild, transient	Moderate	Severe	Intractable
Fatigue	Symptomatic, fully ambulatory	Symptomatic, in bed <50% of time	Symptomatic, in bed >50% of time, not bedridden	100% bedridden
Weight loss	2.0 – 2.9%	3.0 – 4.9%	5.0 – 10.0%	> 10.0%
Injection site	Pain, erythmea, surface ecchymosis; no extra factor required	Pain; erythmea, hematoma; factor required	Pain; erythmea, hematoma; factor required; prevents ambulation	Pain; erythmea, hematoma; factor required; prevents ambulation; lasting >3 weeks
Coagulation				
Factor IX inhibitor	0.5 – 4.9 B.U. persisting <3 months	0.5 – 4.9 B.U. persisting >3 months	≥5.0 B.U. persisting <3 months	≥5.0 B.U. persisting >3 months
Hematology				
Leukocytosis	1.5 – 2.0X baseline	2.1 – 2.5X baseline	2.6 – 3.0X baseline	> 3.0X baseline
Thrombocytopenia	40,000 – 50,000/mL	30,000 – 39,999/mL	20,000 – 29,999/mL	< 20,000/mL
Anemia	8.0 – 9.9 g/dL	7.0 – 7.9 g/dL	6.0 – 6.9 g/dL	< 6.0 g/dL
Hepatic				
Elevated Bilirubin	1.2 – 1.5X baseline	1.6 – 2.0X baseline	2.1 – 3.0X baseline	> 3.0X baseline
Elevated Transaminases	2.5 – 2.9X normal	3.0 – 4.9X normal	5.0 – 10.0X normal	> 10.0X normal
Elevated Alkaline Phosphatase	2.0 – 2.9X normal	3.0 – 4.9X normal	5.0 – 10.0X normal	> 10.0X normal
Renal				
Elevated Creatinine (mg/dL)	1.1 – 1.5X normal	1.6 – 2.0X normal	2.1 – 3.0X normal	> 3.0X normal
Proteinuria	1+	2 – 3+	4+	Nephrotic syndrome
Hematuria	Micro only	Gross no clots	Gross + clots	Requires transfusion
Gastrointestinal				
Appetite	Normal intake	Intake significantly decreased but can eat	No significant intake	Requires transfusion
Nausea/vomiting	Nausea alone	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Diarrhea	Transient <2 days; freq loose BM <4/day; no therapy required	Tolerable but > 2 days; freq loose BM >4/day; relief with therapy	Intolerable or bloody diarrhea; no relief with therapy	Dehydration and hospitalization
Pulmonary				
Respiratory symptoms	Mild (eg, 1 flight SOB)	Exertional dyspnea (eg, SOB while walking)	Dyspnea at rest	Complete bed rest; Continuous assisted O_2 ventilation
Chest X-Ray	Localized increase in lung markings	Multi-focal increase in lung markings	Increase in lung markings with focal infiltrate	Mutillobar infiltrates
PFTs (FEV, FVC)	10 – 15% decline	16 – 20% decline	21 – 25% decline	> 25% decline
Skin/Allergy				
Cutaneous and Allergy	Transient erythema	Dry desquamation, vesiculation, pruritis or phlebitis; urticaria	Moist desquamation; serum sickness	Exfoliative dermatitis; anaphylaxis
Metabolic				
Hyperglycemia	120 -160 mg/dL	161 – 250 mg/dL	251 – 500 mg/dL	>500 mg/dL or diabetic ketoacidosis
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL
Hypocalcemia	8.3 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	<6.0 mg/dL
Hyperkalemia	5.1 – 5.4 mg/dL	5.5 – 5.9 mg/dL	6.0 – 6.4 mg/dL	>6.4 mg/dL

Central Nervous System				
Headache	Mild, transient, no therapy required	Analgesic required	Narcotic required	Intractable
Mental status	Mild somnolence, agitation or confusion	Moderate somnolence, agitation or confusion	Severe somnolence, confusion, disorientation, hallucination	Coma, seizures, toxic psychosis
Motor	Subjective weakness, no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
Sensory	Mild paresthesia, loss of DTRs	Mild or moderate objective sensory loss, moderate paresthesia	Severe objective sensory loss or paresthesia that interferes with function	
Cardiovascular				
Cardiac symptoms	Asymptomatic but abnormal cardiac sign	Transient symptoms; no therapy required	Symptomatic but responds to therapy	Symptomatic & no response to therapy
Ischemia	Non-specific ST or T wave changes	Asymptomatic, ST and T wave changes suggesting ischemia	Angina without evidence of infarction	Acute myocardial infarction
Hypertension	Asymptomatic, transient increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL; No treatment required	Recurrent or persistent increase by greater than 20 mm Hg (D) or to >150/100 if previously WNL. No treatment required	Requires therapy	Hypertensive crisis
Hypotension	Clinically significant changes requiring no therapy (including transient orthostatic hypotension)	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization; resolves within 48 hours of therapy	Requires therapy and hospitalization; requires >48 hours of therapy

Freq = frequent; BM = bowel movements; DTR = deep tendon reflexes; SOB = shortness of breath; WNL = within normal limits

10.9. Appendix 9: Abbreviations

AASLD	American Association for the Study of Liver Diseases
AAV	adeno-associated virus vector
AAV2	adeno-associated virus vector, serotype 2
AAV8	adeno-associated virus vector, serotype 8
AAV-hFIX	adeno-associated viral vector expressing human factor IX
AAV2-hFIX16	single-stranded adeno-associated viral vector, serotype 2, expressing human factor IX under control of the human α1-antitrypsin promoter coupled to the human apolipoprotein E hepatic locus control region
AAV8-hFIX19	single-stranded adeno-associated viral vector, serotype 8, expressing human factor IX under control of the human α1-antitrypsin promoter coupled to the human apolipoprotein E hepatic locus control region (construct changes from hFIX16 to hFIX19 include codon-optimization, removal of alternate open reading frames of the factor IX gene, and replacement of *amp* with *kan* resistance in the plasmid used for vector generation)
AAV8-LP1-hFIXco	self-complementary AAV vector, serotype 8, expressing human factor IX, used in the St. Jude's/UCL gene therapy trial
AAV-Spark100-hFIX19-Padua	adeno-associated viral vector comprised of the Spark100 AAV capsid encoding hFIX-Padua
ABR	annualized bleed rate
AEs	adverse events
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
amp	ampicillin resistance gene
APRI aPTT	AST-to-platelet ratio index activated partial thromboplastin time
AST	aspartate transaminase
BMI	body mass index
BUN	blood urea nitrogen
CFR CNS	Code of Federal Regulations central nervous system
cp	capsid particles
CPT CRO	common protocol template Contract Research Organization

CSR CT CTL	clinical study report clinical trial cytotoxic T lymphocyte
CVAD	central venous access device
DNA	deoxyribonucleic acid
DMC	data monitoring committee
DILI DRE EAHAD	drug-induced liver injury disease related event European Association for Haemophilia and Allied Disorders
eCRF	electronic case report form
ECG ED EDP	electrocardiogram exposure day exposure during pregnancy
ELISPOT EOS	enzyme-linked immunospot assay end of study
EudraCT FDA	European Clinical Trials Database Food and Drug Administration
FIX	factor IX
FIX:C	Circulating factor IX
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Haem-A-QoL HAL HBV HBsAg	haemophilia A quality of life questionnaire hemophilia activities list hepatitis B virus hepatitis B surface antigen
HCV	hepatitis C virus
hFIX	human coagulation factor IX
HIV HJHS	human immunodeficiency virus hemophilia joint health score
HLA	human leukocyte antigen
HRQoL	health-related quality-of-life
IB ICF	Investigator Brochure Informed Consent Form
ICH	International Council for Harmonisation
ID IEC	Identification independent ethics committee
IFN	interferon
IFN-γ	interferon gamma
IgG4	immunoglobulin G subclass 4
IND	investigational new drug
INR	international normalized ratio
IP IRB	investigational product institutional review board
ISF	investigator site file

IU	international units
IV	intravenous
kan	kanamycin resistance gene
LDH	lactate dehydrogenase
LFT	liver function test
LSLV	last subject last visit
LTFU	long-term follow-up
MHC	major histocompatibility complex
NAb	neutralizing antibody
NHP	non-human primate
PBMC	peripheral blood mononuclear cells
PCD	primary completion date
PCR	polymerase chain reaction
pd	plasma derived
pd-FIX	plasma-derived factor IX
PK PO	pharmacokinetic orally
PT	prothrombin time
QD	once a day
QoL rFIX	quality of life recombinant factor IX
RNA	ribonucleic acid
ROTEM	rotational thromboelastogram
SAE	serious adverse event
SAP SJ-UCL	statistical analysis plan St. Jude Children's Research Hospital – University College London
SOP	standard operating procedure
PF-06838435	adeno-associated viral vector with FIX gene (AAV-Spark100-hFIX19-Padua)
SUSAR	suspected unexpected serious adverse reaction
TAT	thrombin-antithrombin
TBili TEG	total bilirubin thromboelastography
TGA	thrombin generation assay
T_{max}	Time at maximum activity
ULN	upper limit of normal
vg	vector genome
WBC	white blood cell
WNL	within normal limits
WT	wild-type

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