Protocol C0371002

Phase 3, Open-Label, Single-Arm Study to Evaluate Efficacy and Safety of FIX Gene Transfer with PF-06838435 (rAAV-Spark100-hFIX-R338L) in Adult Male Patients with Moderately Severe to Severe Hemophilia B (FIX:C≤2%) (BeneGene-2)

Statistical Analysis Plan (SAP)

Version: 6

Date: 07 Jul 2022

TABLE OF CONTENTS

LIST OF TABLES 5
LIST OF FIGURES 5
APPENDICES 5
1. VERSION HISTORY 6
2. INTRODUCTION 9
2.1. Study Objectives, Endpoints, and Estimands 10
2.1.1. Primary Estimand(s) 14
2.1.2. Secondary Estimand(s) 15
2.1.2.1. ABR for Treated Bleeds 15
2.1.2.2. Annualized Infusion Rate (AIR) 15
2.1.2.3. FIX:C 16
2.1.2.4. Annualized FIX consumption 16
2.1.2.5. Other Secondary Endpoints 16
2.2. Study Design 18
3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 18
3.1. Primary Endpoint(s) 18
3.1.1. Annualized Bleeding Rate (ABR) for Total Bleeds 18
3.2. Secondary Endpoint(s) 20
3.2.1. ABR for Treated Bleeds 20
3.2.2. Annualized Infusion Rate (AIR) 20
3.2.3. FIX:C 21
3.2.4. Annualized FIX Consumption 22
3.2.5. Annualized Bleeding Rate of Specific Type of Bleeding 22
3.2.6. Percentage of Participants Without Bleeds 22
3.2.7. Hemophilia Joint Health Score (HJHS) 23
3.2.8. Patient-Reported Outcome Assessments 23
3.2.8.1. Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) 23
3.2.8.2. Hemophilia Activities List (HAL, v2) 24
3.2.9. Immunogenicity 25

3.3. Other Endpoint(s) 25
3.3.1. Joint Assessments 25
3.3.1.1. Target Joints 25
3.3.1.2. X-ray Assessments to Evaluate Joints 25
3.3.1.3. Magnetic Resonance Imaging (MRI) to Evaluate Joints 25
3.3.2. Additional PRO Assessments 26
3.3.2.1. Hemophilia Life Impacts Questionnaire (HLIQ) 26
3.3.2.2. EQ-5D-5L 26
3.3.3. Vector Shedding 27
3.3.4. FIX Antigen Levels and Coagulation Activation Tests 27
3.4. Baseline Variables and Covariates 28
3.5. Safety Endpoints 28
3.5.1. Adverse Events 28
3.5.2. Laboratory Data 29
3.5.3. Vital Signs and Other Safety Endpoints 30
3.5.4. Concomitant Medication 30
3.5.5. Liver Ultrasound 30
4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS) 30
5. GENERAL METHODOLOGY AND CONVENTIONS 31
5.1. Hypotheses and Decision Rules 33
5.2. General Methods 34
5.2.1. Analyses for Binary Endpoints 35
5.2.2. Analysis for Count Endpoints 36
5.2.3. Analyses for Continuous Endpoints 36
5.2.4. Analyses for Categorical Endpoints 36
5.3. Methods to Manage Missing Data 36
6. ANALYSES AND SUMMARIES 36
6.1. Primary Endpoint(s) 36
6.1.1. ABR for Total Bleeds 36
6.1.1.1. Main Analysis 36
6.1.1.2. Supplementary Analysis 37

6.2. Secondary Endpoint(s) 38
6.2.1. ABR for Treated Bleeds 38
6.2.2. AIR 38
6.2.2.1. Main Analysis 38
6.2.2.2. Sensitivity/Supplementary Analysis 39
6.2.3. FIX:C 39
6.2.3.1. Main Analysis 39
6.2.3.2. Sensitivity/Supplementary Analyses 40
6.2.4. Annualized FIX Consumption 40
6.2.5. Annualized Bleeding Rate of Specific Type 40
6.2.6. Percentage of Participants without Bleeding 41
6.2.7. Hemophilia Joint Health Score (HJHS) 41
6.2.8. Patient-Reported Outcomes 41
6.2.8.1. Haem-A-QoL 41
6.2.8.2. Hemophilia Activities List (HAL, v2) 42
6.2.9. Immunogenicity 42
6.3. Other Endpoint(s) 42
6.3.1. Joint Assessments 42
6.3.1.1. Target Joints 42
6.3.1.2. X-ray Assessments to Evaluate Joints 43
6.3.1.3. Magnetic Resonance Imaging (MRI) to Evaluate Joints 43
6.3.2. Additional Patient-Reported Outcomes 43
6.3.2.1. Patient Global Impression of Change – Hemophilia (PGIC-H) 43
6.3.2.2. Hemophilia Life Impacts Questionnaire (HLIQ) 43
6.3.2.3. EQ-5D-5L 44
6.3.3. Vector Shedding 44
6.3.4. FIX Antigen Levels and Coagulation Activation Tests 44
6.4. Subset Analyses 44
6.5. Baseline and Other Summaries and Analyses 45
6.5.1. Baseline Summaries 45
6.5.2. Study Conduct and Subject Disposition 45

6.5.3. Study Treatment Exposure 45
6.5.4. Concomitant Medications and Nondrug Treatments 45
6.6. Safety Summaries and Analyses 45
6.6.1. Adverse Events 45
6.6.2. Laboratory Data 46
6.6.3. Vital Signs/Physical Examination/Other Safety Outcome 46
6.7. COVID-19 Related Data Listings and Summaries 46
7. INTERIM ANALYSES 47
7.1. Introduction 47
8. APPENDIX 48
9. REFERENCES 52

LIST OF TABLES

Table 1. Summary of Changes 6
Table 2. Sequence of Gatekeeping Process of Multiple Hypothesis Tests 33

LIST OF FIGURES

Figure 1. Phase 3 Study 18
Figure 2. Adverse Events to be Included in the Short Term and Long-Term Summary 29

APPENDICES

Appendix 1. Statistical Methodology Details 49
Appendix 1.1. Example of SAS Code of Repeated Measure Additive Negative Binomial Regression Model: 49
Appendix 1.2. Example of SAS Code of Repeated Measure Negative Binomial Regression Model with log link: 49
Appendix 2. List of Abbreviations 50

1. VERSION HISTORY

This statistical analysis plan (SAP) for Study C0371002 is based on the protocol dated 29 Jun 2022.

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1/19 Feb 2019	Original	Not applicable (N/A)	N/A
2/ 24 Sep 2020	Protocol Amendment 1 23 Jun 2020	Update to reflect changes in Protocol Amendment.	**The following changes have been made according to Protocol Amendment 1:** Updated endpoints and estimand definition: 1. Updated adverse events of special interest (AESI) and immunogenicity related endpoints. 2. Added clarification on secondary and tertiary/exploratory endpoints of Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) and Haemophilia Activities List (HAL). 3. Removed Patient Global Impression of Change – Hemophilia (PGIC-H) from secondary endpoints. 4. Added thrombin antithrombin level (TAT) as a tertiary endpoint. **The following changes were also made:** 1. Modified definition of baseline annualized bleeding rate (ABR) and annualized infusion rate (AIR) to include the screening period in C0371002. 2. Added definition of X-ray substudy analysis population. 3. Pulled out anchor analysis for the patient reported outcomes (PRO) endpoints as these are described in a supplemental SAP. 4. Removed the "within-subject comparison" terminology for testing of ABR to clarify the test is on model-based estimates of pre- and post-infusion values. 5. Added definition of Year 6 (>Month 60 to Month 72). 6. Clarified that an eDiary case report form (CRF) will also be included for deriving ABR and AIR (Section 3.1.1). 7. Added clarification about algorithm of deriving treated bleed (Section 3.1.1). 8. Added analysis of yearly totals for percentage of participants without bleeds (Section 3.2.6). 9. Added details about missing data handling for Haem-A-QoL and HAL (Section 3.2.8).

			10. Moved immunogenicity to a standalone section, and added details about the analyses with enzyme-linked immunosorbent spot (ELISPOT) data (Section 3.2.9 and Section 6.2.9). 11. Updated details about baseline definition for X-ray and magnetic resonance imaging (MRI) assessments of joints (Section 3.3.1). 12. Added definition of index score (total score) for EQ-5D-5L (Section 3.3.2.2) 13.Added details about vector shedding analyses (Section 3.3.3 and Section 6.3.3). 14. Moved factor IX (FIX) antigen levels and coagulation activation tests to a standalone section (Section 3.3.4 and Section 6.3.4). 15. Added details about the definition of treatment emergent adverse events (TEAE) (Section 3.5.1). 16. Moved immunogenicity endpoints to Section 3.2.9 and added α-fetoprotein (Section 3.5.2). 17.Added liver ultrasound assessment (Section 3.5.5). 18. Clarified timing for the interim analysis and the primary analysis and the gatekeeping strategy (Section 5). 19.Added details about windowing of visits in Section 5.2. 20.Added categorical summary of circulating factor IX (FIX:C) >15% (Section 1.1.1.1). 21.Corrected that the upper bound of the 95% confidence interval (CI) of the difference in ABR will be compared to the noninferiority (NI) margin (Section 6.1.1.1). 22.Added a sensitivity analysis to impute ABR after resumption of FIX factor replacement. 23.Added a sensitivity analysis to use the pre-treatment ABR from the most recent 6 months prior to infusion as the comparison group. 24.Added details about data presentation in Section 6.5.2 and 6.5.3. 25. Added details about data summaries for corticosteroid use and ELISPOT analysis (Section 6.6.2). 26.Added data presentations to evaluate Coronavirus disease 2019 (COVID-19) impact.
3/ 25 Mar 2021	Protocol Amendment 1 23 Jun 2020	Added additional sensitivity analyses according to EMA's requests and provided additional clarification.	1. Clarified steady state FIX calculation is from Day 82. 2. Clarified bleed definition (Section 3.1.1). 3. Added the exploratory analysis for vector shedding to the primary analysis/IA 4. Added categorical summary of steady state FIX with 5 groups (Section 1.1.1.1). 5. Clarified that model-derived mean ABR and its 95% CI are to be presented in summary

			tables and added the percentage reduction and 95% CI (Section 6.1.1.1 and Section 6.1.1.2). 6. Added summary of % reduction and 95% CI for AIR (Section 6.2.2.1). 7. Added sensitivity analyses (Section 6.1.1.2 [ABR] and Section 6.2.2.2 [AIR]).). 8. Added summary of subjects with target joints and newly developed target joints (Section 6.3.1.1). 9. Removed summary of dimension score and added summary of number and percentage of participants in each health status category for EQ-5D-5L (Section 6.3.2.3 and Section 6.3.2.3). 10. Added clarification on analysis population at interim analysis (Section 7).
10 Aug 2021/v4.0	Protocol Amendment 2 09 Aug 2021	Changed the time point for interim analysis and the analysis period for the co-primary endpoints, the key secondary endpoint, and bleed related secondary endpoints based on FDA request that analysis is performed 12 months post-steady state versus 12 months post-infusion.	1. Exchanged "Padua" to "R338L" for reference of the variant. 2. Changed the time point for interim analysis and primary analysis to 15 months post infusion (Section 5 and Section 7). 3. Updated the analysis period for co-primary endpoints, key secondary endpoints, and any bleed related secondary endpoints (Section 2, Section 3.1, Section 3.2.1, and Section 3.2.6). 4. Added clarification for new untreated bleed (Section 3.1.1). 5. Updated analysis population to Dosed with 15-month follow up (Section 4). 6. Updated analysis window (Section 5.2). 7. Added sensitivity analysis comparing pre-treatment ABR to ABR from Week 12 to Month 15 (Section 6.1.1.2). 8. Updated analysis window from 1 year to 15 months for FIX:C, ABR and AIR (Sections 6.1, 6.2.1, and 6.2.6). 9. Added summary of participants who resumed FIX prophylaxis resumption by time interval (Section 6.2.2.2). 10. Removed summary of AE after year 1 (Section 6.6.1). 11. Removed data listings for PF-06838435 and summary of physical examination for Safety Population (Section 6.5.3 and Section 7.1). 12. Other minor typographical updates.
13 Oct 2021/v5.0	Protocol Amendment 2 12 Oct 2021	Updated to reflect changes within the protocol (Removed interim analysis, and added ABR for total bleeds as key	1. Added ABR for total bleeds as a key secondary endpoint (Section 2.1, Section 5.1, and Section 6.2.2). 2. Clarified the co-primary endpoint of ABR is for treated bleeds and added clarification about date of FIX prophylaxis resumption (Section 3.1.1).

		secondary endpoint); reduced sensitivity analyses; provided additional clarification.	3. Removed interim analysis (Section 5.1, Section 7.1). 4. Removed "Dosed with 15 months follow up Analysis Set" and clarified Evaluable Analysis Set definition (Section 4). 5. Removed sensitivity analysis in the Evaluable population (Section 6.1.1.2, 6.2.2.2, 6.2.5 and 6.2.6). 6. Removed sensitivity analysis on AIR excluding perioperative infusions (Section 6.2.2.2). 7. Updated target joint analysis (Section 6.3.1.1). 8. Updated figure in Appendix 1.1.
07 Jul 2022/v6.0	Protocol Amendment 3 29 Jun 2022	Updated to reflect changes within the protocol (changed primary endpoint to ABR_{total}, FIX:C and ABR_{treat} moved to key secondary endpoints, and primary analysis period change to Week 12 to Month 15)	1. Updated the primary analysis period for ABRtotal, ABRtreat, AIR, FIX:C and FIX consumption to begin at Week 12 and conclude at Month 15 throughout the document. 2. Updated primary endpoint to ABR_{total} (Sections 2.1.1, 3.1, 5 and 6.1). 3. Moved ABR_{treat} to key secondary endpoint (Sections 2.1.2.1, 3.2.1, 5 and 6.2.1). 4. Moved FIX:C to key secondary endpoint and added descriptive analysis by study visit (Sections 2.1.2.3, 3.2.3, 5 and 6.2.3). 5. Added analysis by corticosteroid period (Sections 5.2, 3.1, 3.2.3 and 6.1.1.2). 6. Added clarification about peak value definition and handling of BLoQ values for vector shedding analysis (Sections 3.3.3 and 6.3.3). 7. Added clarification about washout rule for FIX antigen (Section 3.3.4). 8. Updated testing hierarchy (Section 5.1). 9. Updated windowing for FIX:C (Section 5.2). 10. Clarified summaries for corticosteroid duration (Section 6.6.2). 11. Removed Appendix 1.1 Derivation of ABR/AIR definition. 12. Removed Appendix 1.2 Haemophilia Activities List – Adults

2. INTRODUCTION

PF-06838435 (generic name: fidanacogene elaparvovec; formerly known as SPK 9001 or rAAV Spark100-hFIX-Padua, which is also referred to as Spark100-hFIX-R338L) is an adeno-associated viral (AAV) vector designed to drive expression of the human factor IX-R338L (hFIX-R338L) transgene and raise the circulating levels of factor IX (FIX:C).

C0371002 is a single-arm pivotal phase 3 study designed to evaluate clinical efficacy and safety of PF-06838435 in adult male participants with moderately severe or severe

hemophilia B (FIX:C ≤2% or ≤2 international units per deciliter [IU/dL]) for the study duration of 6 years after a single administration of the study treatment. The primary efficacy endpoint of C0371002 is annualized bleeding rate (ABR) for total bleeds (treated and untreated) (referred to as ABR_{total} hereafter in this document) from Week 12 [Week 12 ± 2 days of visit window, Day 82] to Month 15 [Week 65 ±2 weeks of visit window, Day 469]. The study will enroll eligible participants who have completed at least 6 months of routine prophylaxis in the C0371004 study. The bleeding and factor IX (FIX) infusion data prior to PF-06838435 infusion (consisting of data collected in C0371004 and during the period prior to study drug infusion in C0371002, referred to as "Pre-Infusion Period" hereafter in this document) will serve as the control to be compared to bleeding and FIX infusion data post PF-06838435 infusion in C0371002.

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study C0371002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. A separate SAP will be prepared, describing the anchor-based approach for evaluating the meaningful within-patient change (MW-PC) for Haem-A-QoL, HAL and HLIQ based on Patient Global Impression of Change – Hemophilia (PGIC-H).

Any deviations from this analysis plan will be described in the Clinical Study Report.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (circulating factor IX [FIX:C] ≤2%).	Primary endpoint: • Noninferiority of annualized bleeding rate (ABR) for total bleeds (treated and untreated) from Week 12 to Month 15 vs standard of care (SOC) coagulation factor IX (FIX) prophylaxis regimen, comparing pre- and post PF-06838435 infusion.
Secondary	
• Key objective: To demonstrate the efficacy of PF-06838435 in terms of the use of treated bleeds, exogenous FIX, and FIX:C.	Key endpoints: • Noninferiority on ABR for treated bleeds from Week 12 to Month 15 vs SOC FIX prophylaxis replacement

	regimen, comparing pre- and post PF-06838435 infusion. • Annualized infusion rate (AIR) of exogenous FIX from Week 12 to Month 15 vs AIR of FIX with SOC FIX replacement regimen pre PF-06838435 infusion. • Mean vector-derived FIX:C level at steady state (from Week 12 to Month 15) demonstrated to be greater than 5%. FIX:C will also be summarized descriptively by study visit.
• To compare additional efficacy parameters post PF-06838435 infusion to baseline in order to further characterize PF-06838435 treatment, including use of exogenous FIX, information on bleeding events, and patient-reported outcomes addressing health-related quality of life, activities of daily living and general health status.	The following parameters will be compared with exogenous FIX prophylaxis replacement regimen, using post PF-06838435 infusion data from Week 12 to Month 15. • Annualized FIX consumption. • Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated. • Frequency of target joint bleeds. • Percentage of the participants without bleeds. The following parameters will be compared with SOC FIX replacement regimen, comparing pre- and post PF-06838435 infusion at 12 months: • Change in joint health as measured by the Hemophilia Joint Health Score (HJHS) instrument. • Patient-Reported Outcomes (PROs) instruments:

	• Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain; • Haemophilia Activities List (HAL) Complex Lower Extremity Activities component score

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

• Assess durability of efficacy up to 6 years.	The following parameters will be assessed throughout the 6-year study period according to the schedule of activities (SoA). Summaries will be provided for the

	overall follow-up period, as well as by yearly intervals: • ABR for total bleeds (treated and untreated) • AIR of exogenous FIX; • ABR for treated bleeds • Vector-derived FIX:C level by study visit and the geometric mean at each yearly interval • Annualized FIX consumption; • Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated.; • HJHS total score • Frequency of target joint bleeds • PRO instruments: • Haem-A-QoL Physical Health domain • HAL Complex Lower Extremity Activities component score
Tertiary/Exploratory	
• Pharmacodynamics of PF-06838435.	• Vector shedding of PF-06838435 as measured by quantitative polymerase chain reaction (qPCR) in plasma, saliva, peripheral blood mononuclear cells (PMBC), urine, and semen until 3 consecutive specimens test negative for the given specimen type. • FIX antigen levels.
• To compare joint health post PF-06838435 infusion to baseline.	• Number of target joints.

	• Joint status as assessed by X-ray in some participants who consent to participate in an optional substudy. • Joint status as assessed by magnetic resonance imaging (MRI) in a subset of some participants who consent to participate in an optional substudy.
• Impact on coagulation.	• Coagulation activation tests: activated partial thromboplastin time (aPTT), international normalized ratio (INR), D-dimer, thrombin generation assay (TGA) , and thrombin antithrombin level (TAT). • Correlation of FIX:C between one-stage assay and chromogenic assay.
• To compare additional efficacy parameters post PF-06838435 infusion in order to further characterize PF-06838435 treatment in terms of patient-reported outcomes assessing hemophilia life impacts and global health status.	• PRO instruments: Haem-A-QoL (domains not previously specified), HAL (scores not previously specified), Hemophilia Life Impacts Questionnaire (HLIQ) and EuroQol, 5 dimensions, 5 levels (EQ-5D-5L), in the first 12 months and annually in the follow-up period, Years 2 to 6.

2.1.1. Primary Estimand(s)

The primary objective is addressed via assessment of the primary endpoint of ABR_{total} from Week 12 to Month 15 after PF-06838435 infusion. Efficacy is summarized by the difference between ABR_{total} pre- and post PF-06838435 infusion; pre-treatment data will be obtained from Pre-Infusion Period. The estimand includes the following 4 attributes:

- Population: male adults with moderately severe to severe hemophilia B (FIX:C ≤2%) who have received infusion of PF-06838435.
- Variables:
  - ABR_{total} comparing pre PF-06838435 infusion from the Pre-Infusion Period to post PF-06838435 infusion from Week 12 to Month 15 .

- Intercurrent event(s): Since no more than the single dose of PF-06838435 infusion on Day 1 will be administered during the study, there should be no treatment discontinuations. Prophylaxis FIX replacement regimen may be resumed if treatment with PF-06838435 is not efficacious. Once prophylaxis FIX replacement is re-established, the data will not reflect the efficacy of study treatment assessments and therefore data following resumption of FIX prophylaxis regimen will be excluded. Further details of handling intercurrent events are discussed in Section 3 for each of the endpoints.

- Population-level summary: difference in mean ABR_{total} pre PF-06838435 infusion vs. ABR_{total} from Week 12 to Month 15.

There may be missing data from participants lost to follow up, but it is anticipated to be rare. The primary endpoint, ABR_{total} from Week 12 [Day 82] to Month 15 [Day 469]) will utilize all applicable data to define the endpoint, with the exceptions as discussed in Section 3 . There will be no imputation for missing data for the primary analysis.

2.1.2. Secondary Estimand(s)

2.1.2.1. ABR for Treated Bleeds

The key secondary endpoint, ABR for treated bleeds, is defined similarly as the primary endpoint ABR_{total}, except that only treated bleeds will be counted, and will be referred as ABR_{treat} hereafter in this document. The estimand follows the same approach as described for ABR_{total}. A noninferiority test of treatment difference in ABR_{treat} between pre- and post treatment with PF-06838435 will be performed similarly as the primary endpoint ABR_{total}, with a NI margin of 3.

2.1.2.2. Annualized Infusion Rate (AIR)

The key secondary endpoint, AIR of exogenous FIX from Week 12 to Month 15 will be tested for superiority vs AIR with FIX prophylaxis replacement regimen during the Pre-Infusion Period.

- Population: Patients who are male adults with moderately severe to severe hemophilia B (FIX:C ≤2%) who have received infusion of PF-06838435.

- Variable: AIR of exogenous FIX pre-PF-06838435 infusion and from Week 12 to Month 15 post PF-06838435 infusion

- Intercurrent event(s): Resumption of FIX prophylaxis does not affect this analysis. This endpoint includes all infusions during the observation period regardless of purpose of FIX replacement therapy, i.e., includes infusions to treat bleeding, procedure related, for preventive purpose, or for prophylaxis regimen, etc.

- Population-level summary: Difference in mean AIR comparing AIR from Week 12 to Month 15 post PF-06838435 infusion to AIR during the Pre-Infusion Period.

2.1.2.3. FIX:C

The key secondary endpoint, steady state FIX:C from 12 weeks [Day 82] to Month 15 [Day 469] after PF-06838435 infusion, is to be compared to a fixed threshold of 5%. The estimand includes the following 4 attributes:

- Population: male adults with moderately severe to severe hemophilia B (FIX:C ≤2%) who have received infusion of PF-06838435.

- Variables: Geometric mean of all valid measurements of FIX:C following steady state (defined as 12 weeks [Day 82]) to Month 15 [Day 469] inclusive post PF-06838435 infusion);

- Intercurrent event(s): During the study, participants are requested to suspend their prophylaxis FIX replacement regimen. Only on-demand FIX replacement is permissible for the treatment of bleeding events as defined in Protocol Section 6.5.1. Any sample taken within 7 days after (14 days if Extended half-life [EHL] product is used) exogenous FIX replacement therapy administered for any purpose (including treatment of bleeding, preventive purpose, or resumption of FIX prophylaxis regimen) will be excluded from the analysis of FIX: C. Once prophylaxis FIX replacement is re-established, FIX:C data at the visits following resumption of FIX prophylaxis regimen will be imputed as 1.9%, slightly below the baseline value (2%) to be conservative. Further details of handling intercurrent events are discussed in Section 3.

- Population-level summary: population mean of the individual participant geometric mean FIX:C. In addition, absolute value of FIX:C will be summarized over time by study visit. Data from all three assays (one-stage assay with Actin reagent, one-stage assay with SynthAsil reagent, and chromogenic assay) will be presented.

2.1.2.4. Annualized FIX consumption

Annualized FIX consumption is similarly defined as that for AIR, except that the consumed dose in the unit of international units per kilogram (IU/kg) and total units will be measured, while AIR only counts frequency of doses. The estimand for the additional secondary objective and associated secondary endpoint, annualized FIX consumption, follows the same approach as described for AIR. A superiority hypothesis test will be performed, comparing data obtained from Pre- and Post-Infusion Period.

2.1.2.5. Other Secondary Endpoints

Other secondary endpoints, such as annualized number of bleeding events (ABR_{total}) of specific type, (spontaneous and traumatic; and untreated bleeding), frequency of target joint bleeds and percentage of the participants without bleeds, will handle intercurrent events in the same way as described for ABR_{total}.

The following parameters will be compared pre PF-06838435 infusion and 12 months post PF-06838435 infusion. The comparisons should reflect general health modification of hemophilia patients.

- Change in joint health as measured by the Hemophilia Joint Health Score (HJHS) instrument.
- Patient Reported Outcomes (PRO) instruments:
    - Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health domain;
    - Haemophilia Activities List (HAL) Complex Lower Extremity Activities Component Score;

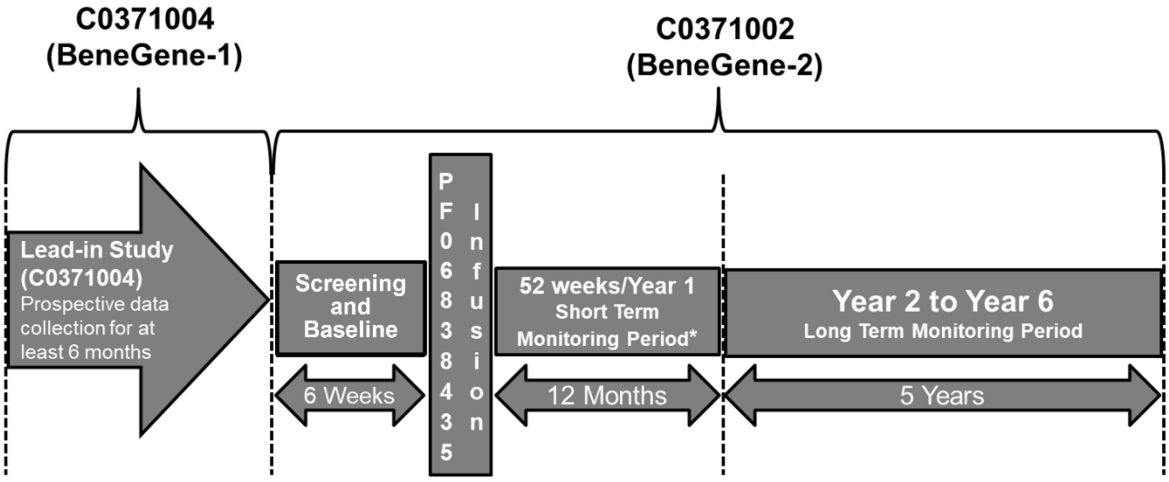
Secondary endpoints include the following parameters assessed throughout the 6-year study period according to the Schedule of Activities (SoA), which evaluate the long-term efficacy of gene therapy treatment for hemophilia. Summaries will be provided for the overall follow-up period, as well as by yearly intervals.

- ABR for total bleeds (treated and untreated);
- ABR for treated bleeds;
- AIR of exogenous FIX;
- Vector-derived FIX:C level by study visit and the geometric mean at each yearly interval.
- Annualized FIX consumption;
- Annualized number of bleeding events of specific type: spontaneous and traumatic, and untreated bleeding;
- Percentage of participants without bleeds (total bleeds and treated bleeds);
- HJHS total score;
- Frequency of target joint bleeds;
- PROs instruments:
    - Haem-A-QoL, Physical Health domain;
    - HAL Complex Lower Extremity Activities Component Score

2.2. Study Design

This phase 3, open-label, single arm, multi-site study will compare the efficacy following a single intravenous (IV) infusion of PF-06838435 to FIX prophylaxis in the usual care setting, in adult male participants from the lead-in study (C0371004) with severe to moderately severe hemophilia B (FIX:C ≤2%). Eligible study participants will have completed a minimum 6 months of FIX replacement prophylaxis therapy in the lead-in study (C0371004). The study duration for each participant in this study (C0371002) will be 312 weeks. At least 50 participants who completed study C0371004 will be screened to dose at least 40 participants with PF-06838435, and all participants who are dosed in C0371002 are expected to be evaluable.

Figure 1. Phase 3 Study



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

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

ABR_{total} from Week 12 to Month 15 is the primary endpoint of this study.

3.1.1. Annualized Bleeding Rate (ABR) for Total Bleeds

An eDiary, a hand-held device, will be provided to all participants at Visit 1. The participants are required to enter any occurrence of bleeding episodes (including date, time, location, and etiology) and any exogenous FIX replacement (including date, time, reason, and dose) required to treat the bleeds. If bleeding episodes or treatments are not entered in the eDiary during the appropriate time window or due to extenuating circumstances, data should be entered by the investigator (or appropriate site staff member) into a Bleeding case report form (CRF) with appropriate source documentation in the participant's medical record.

When calculating ABR, bleeds will be pooled from both sources (eDiary and Bleeding CRF) to avoid missing reports.

The identification of a new treated bleeding episode is clarified in the Protocol Appendix 7. If a bleed is treated with FIX infusion (according to Bleeding eDiary or Bleeding CRF) within 72 hours post the start of bleeding (by comparing date/time of bleeding to date/time of infusion in Infusion eDiary or Infusion CRF), regardless of the type of treatment (preventive, prophylaxis or rescue medication), it will be considered as a treated bleed. If a bleed is not treated with FIX infusion according to the Bleeding eDiary or the Bleeding CRF, the bleed will not be considered as a treated bleed but considered as an untreated bleed.

For treated bleed, if there are multiple concurrent bleeds (spontaneous or traumatic) on the same date AND time but in different locations in a participant, they will be recorded as one bleed for that participant. However, the bleed will be counted towards all attributable locations in summaries of bleeds of specific site. If concurrent bleeds occurred on the same day but different times and different locations, they will be counted as independent bleeds. On the other hand, if concurrent bleeds occurred on the same day but different times at the SAME location, they will be counted as one bleed.

A bleed is considered a "new untreated bleed" if occurring >72 hours after the previous untreated bleed at the same site or occurring > 72 hours after stopping treatment from the original bleed for which treatment was initiated, or an untreated bleed occurring at a different site from the original bleed regardless of the time (Protocol Appendix 7).

For untreated bleed, every occurrence will be counted as a separate bleed.

The number of bleeding episodes (treated and untreated, excluding procedural bleeds) from Week 12 to Month 15 will contribute to the post-infusion ABR_{total} calculation for each participant, which is the primary endpoint of this study. A noninferiority test of treatment difference in ABR_{total} between pre- and post-infusion with PF-06838435 will be performed, with a NI margin of 3. The endpoint of ABR_{total} will also be calculated for the following designated time periods, such as >Month 15 to Month 24; >Month 24 to Month 36; >Month 36 to Month 48; >Month 48 to Month 60, and >Month 60 to Month 72, and considered as secondary. These secondary endpoints will be referred to as ABR_{total} Year 2, ABR_{total} Year 3, ABR_{total} Year 4, ABR_{total} Year 5, and ABR_{total} Year 6 hereafter in this document.

In addition, ABR_{total} will also be calculated and summarized for the following periods: prior to corticosteroid initiation, during corticosteroid treatment and post-corticosteroid treatment (Section 5.2) for participants in whom corticosteroid are initiated. ABR_{total} during the overall time period (Week 12 to Month 15) for participants who do not have corticosteroid treatment will be presented side by side in the same table.

For participants with incomplete data for the analysis time period, or if a participant has not yet been followed for the full length of the analysis time period, all available data during the analysis period will be annualized and summarized as such. ABR_{total} for each participant will be calculated as below:

$$ABR_{total} = \frac{\text{(Number of bleeding episodes (treated and untreated, excluding procedural bleeds) on study during the given time period) x 365.25}}{\text{(Date of last day – date of first day +1) in that time period}}$$

Bleeding episodes associated with a surgical procedure (perioperative and/or during the surgical rehabilitation period) will not be included in the ABR_{total} calculation.

If prophylaxis FIX regimen is resumed for a participant as defined in Protocol Section 6.5.1, then the time period following the resumption of the prophylaxis regimen will be excluded from the ABR endpoint calculation, which means the bleeding events will be excluded and the time period of observation will be deducted as well. Date and reason of investigator decision to resume FIX prophylaxis will be collected in a CRF. Date of investigator decision will be considered as date of FIX prophylaxis resumption.

The baseline ABR data for total bleeds will be calculated using the above formula and will be based on data collected in the Pre-Infusion Period while participants were on their respective usual care prophylaxis FIX replacement regimen. The baseline ABR will be annualized using the above formula counting bleeds and days in both the lead-in study (C0371004) and the screening period in C0371002 (from date of consent to date of study drug infusion).

3.2. Secondary Endpoint(s)

3.2.1. ABR for Treated Bleeds

ABR_{treat} from Week 12 to Month 15 is defined similarly as ABR_{total} except that only treated bleeding will be counted, and it is a key secondary endpoint. The estimand follows the same approach as described for ABR_{total}. A noninferiority test of treatment difference in ABR_{treat} between pre- and post treatment with PF-06838435 will be performed similarly as ABR_{total}, with a NI margin of 3.

ABR for treated bleeds will also be calculated and analyzed similarly as ABR_{total} for >Month 15 to Month 24; >Month 24 to Month 36; >Month 36 to Month 48; >Month 48 to Month 60, and >Month 60 to Month 72.

3.2.2. Annualized Infusion Rate (AIR)

Annualized infusion rate of exogenous FIX from Week 12 to Month 15 is considered as a key secondary endpoint. All infusions during the observation time period for any purpose including: to treat bleeding, or for preventive purpose, or perioperative, or if prophylaxis FIX regimen is resumed, will be included in the calculation of AIR. Similar endpoints will be calculated for the subsequent time periods, >Month 15 to Month 24; >Month 24 to Month 36; >Month 36 to Month 48; >Month 48 to Month 60; and >Month 60 to Month 72. AIR calculated for the above time period will be referred to as AIR Year 2, AIR Year 3, AIR Year 4, AIR Year 5, and AIR Year 6.

For participants with incomplete data for the analysis time period, or if a participant has not yet been followed for the entire analysis time period, all infusion data during that period will

be included in the analysis and summarized as such. AIR for each participant will be annualized as below:

$$\text{AIR} = \frac{\text{(Number of infusions (for any reason) during the given time period x 365.25)}}{\text{(Date of last day – date of first day +1) in that time period)}}$$

Similarly, the baseline AIR data will be based on data collected in the Pre-Infusion Period while participants were on a prophylaxis FIX replacement regimen. For the baseline AIR calculation, all infusions will be included in the AIR calculation including those to treat bleeding (on-demand), for prophylaxis, for preventive purposes, or perioperative infusions. The AIR baseline will be annualized using the above formula.

The list of participants who resumed FIX prophylaxis and the date of resumption will be confirmed and provided to the programming team by the clinical team before database release. The percentage of the participants who resume a FIX prophylaxis regimen will be determined for the overall time period.

3.2.3. FIX:C

All samples collected from participants for plasma FIX:C as defined in Protocol Section 1.3 SoA will be analyzed both at local and central lab. FIX:C results obtained from local labs will be used for patients care purpose, while the central lab results will be included in the analysis. The certified central clinical laboratory will analyze the sample by two one-stage assays and a chromogenic assay. The first one-stage assay was performed on BCSXP analyzer with Actin-FSL reagent. The second one-stage assay will use the same analyzer but will use 'SynthAsil' as reagent. Data from all three assays will be summarized and presented, while the FIX:C data using one-stage assay (Actin-FSL reagent on BCSXP analyzer), which was also used in the phase 1/2 study C0371005 and long-term follow-up study C0371003, will be the primary result used for hypothesis testing. Any sample taken within 7 days after (14 days if extended half-life [EHL] product is used) exogenous FIX replacement therapy administered for any purpose (including treatment of bleeding, preventive purpose, or resumption of FIX prophylaxis regimen) will be excluded from the analysis of FIX: C.

The steady state FIX:C is calculated for each participant as the geometric mean of all eligible FIX:C measures from 12 weeks [Day 82] to Month 15 [Day 469] inclusive after PF-06838435 infusion. If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the assessments at the visits following withdrawal/dropout/resumption will be imputed as 1.9%. The calculation contains all FIX measurements (scheduled and unscheduled) within the visit window of Week 12 through the visit window of Week 65 (Week 12 ±2 days [Day 82] and Week 65 ± 2 weeks [Day 469]). This key secondary endpoint will be referred to as steady state FIX:C hereafter in this document. For the primary analysis, assessments with missing data imputation will be utilized. Another analysis will also be conducted with only observed data as supportive analysis.

FIX:C will also be analyzed based on all eligible measurements in the designated time periods such as >Month 15 to Month 24; >Month 24 to Month 36; >Month 36 to Month 48; >Month 48 to Month 60, and >Month 60 to Month 72 as secondary endpoints. The geometric mean of all eligible FIX:C measures during the above time periods will be calculated for each individual participant and then summarized across participants. These secondary endpoints will be referred to as FIX:C Year 2, FIX:C Year 3, FIX:C Year 4, FIX:C Year 5, and FIX:C Year 6 hereafter in this document. If a participant has not yet been followed to the full year or has missing data, then all available data for that time interval will be included to calculate geometric mean despite the missed measurements.

The geometric mean of all eligible FIX:C measures will also be calculated and summarized for the following periods: prior to corticosteroid initiation, during corticosteroid treatment and post-corticosteroid treatment (Section 5.2) for participants in whom corticosteroid are initiated. Steady state FIX:C during the overall time period for participants who do not have corticosteroid treatment will be presented side by side in the same table.

In addition, absolute value of FIX:C will be summarized over time by study visit. If multiple assessments exist for a study visit, the average value will be calculated. If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the missing assessment will be imputed as 1.9%. For the primary analysis, assessments with missing data imputation will be utilized for summaries. Another analysis will also be conducted with only observed data as supportive analysis.

3.2.4. Annualized FIX Consumption

Annualized FIX consumption will be reported by IU/kg and total units, and a similar approach of data collection and endpoint derivation as described for AIR will be used. This endpoint of FIX consumption not only measures the number of infusions but also the total units consumed.

3.2.5. Annualized Bleeding Rate of Specific Type of Bleeding

Other secondary endpoints, such as annualized bleeding events (ABR_{total}) of a specific type: by cause: spontaneous, traumatic; by location: in joint (including target joints), in soft tissue, and untreated bleeding, as defined in the Protocol Appendix 7, will be calculated and summarized. The data collection and endpoint derivation are similar to those described for ABR_{total}. The baseline for each specific type of bleeding episode will be derived similarly as defined for ABR_{total}, with baseline of these endpoints obtained from the Pre-Infusion Period. The investigators will assess the health of the joint(s), identified target joints (Section 3.3.1.1) at baseline prior to PF-06838435 infusion. Any bleeding occurring during the study into the identified baseline target joints will be considered as target joint bleeds and will be summarized.

3.2.6. Percentage of Participants Without Bleeds

The percentage of participants without bleeds will be determined for the overall time period, running total (i.e., Week 12 to Month 15, Week 12 to Year 2, Week 12 to Year 3, etc.) and

Week 12 to Month 15, Month 15 to Month 24 (Year 2), and yearly intervals after Month 24. The percentage of participants without bleeding at baseline will be obtained from Pre-Infusion Period, and will also be summarized.

3.2.7. Hemophilia Joint Health Score (HJHS)

A qualified healthcare professional will assess joints to derive modified HJHS, adapted from the original joint scoring system [1]. Six joints (left ankle, right ankle , left elbow , right elbow, left knee, right knee) will be scored on a scale from 0 to 20 according to the following criteria: duration of swelling, muscle atrophy, crepitus, flexion loss, extension loss, instability, joint pain, and strength. Gait will be scored on a scale from 0 to 4 based on walking, stairs, running, hopping on one leg. The total score will be the sum of scores from all joints plus the gait score (range from 0 to 124), with the higher the number equating to more severe joint damage. The HJHS total score is obtained using the following formula excluding the not evaluable (NE) items:

$$\text{HJHS Total Score} = \frac{\text{total score of evaluated items (excluding NE's)}}{\text{possible maximum total score of evaluated items (excluding NE's)}} \times 124$$

HJHS Total Score will not be derived if >20% of items are missing (including NE items). Note: there are 49 individual items to score, therefore 10 or more missing or NE will result in the total score not being calculated.

The baseline assessment is based on the latest evaluation prior to or on the day of PF-06838435 infusion, which is measured during the screening period of Study C0371002.

3.2.8. Patient-Reported Outcome Assessments

PROs should be completed as per SoA using an electronic tablet provided to each site.

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

The Haem-A-QoL Questionnaire is designed for adult (≥17 years) patients with hemophilia. It contains 46 items with ten domains that assess health in the following areas: Physical Health (5 items); Feelings (4 items); View of Self (5 items); Sports and Leisure (5 items); Work and School (4 items); Dealing with Haemophilia (3 items); Treatment (8 items); Future (5 items); Family Planning (4 items); and Partnership and Sexuality (3 items). The total score is also considered.

Each item has a response on the 5-point Likert Scale ranging from “Never” to “All of the time” with several items having a “not applicable” option.

The items prompt the responder to consider life in the last four weeks (“four-week recall”). The items are self-explanatory and the questionnaire can be completed in about 15 minutes.

Scoring is performed by averaging the non-missing item responses for each domain, and then rescaled to be on 0 to 100, with lower scores representing higher quality of life. The total score is directly averaged across the 46 items values and then rescaled on zero to 100.

A domain score can be calculated if ≥50% of that domain's items have been answered.

There is an expectation that the questionnaire is being administered electronically and designed such that patients are not able to skip items. That is, there should not be any missing items unless the participant does not complete the questionnaire.

The Physical Health domain is considered as the primary domain in this questionnaire and is a secondary endpoint, and will be further assessed using the anchor-based method for each yearly visit.

3.2.8.2. Hemophilia Activities List (HAL, v2)

The Hemophilia Activities List (version 2) is a multiple domain measure of the impact of hemophilia on functional abilities in adults. The 7 domains of this instrument contain 42 items in total, as follows: Lying/sitting/kneeling/standing (8); Lower (leg) functioning (9); Upper (arm) functioning (4); Transportation (3); Self-care (5); Household tasks (6); and Sports/Leisure (7). An overall sum score and three component scores can be calculated along with individual domain scores.

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

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

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

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

Each domain or component, or the total, must have a minimum number of valid responses or the score is set to missing. An implication of the "minimum number of valid responses" is that there is an acceptable amount of missing data where the scores (domains, components, and total; score and normalized score) can still be calculated.

The component score of "complex lower extremity activities" is considered the most important in this questionnaire and is a secondary endpoint, and will be assessed using the anchor-based method for each yearly visit. Hemophilia Activities List baseline is the closest evaluation prior to or on the day of PF-06838435 infusion, which is measured during the screening period of Study C0371002. The normalization method to derive score of domains and three components will be used to impute any missing item.

3.2.9. Immunogenicity

Peripheral blood mononuclear cells (PBMCs) result by Interferon gamma (IFN-γ) enzyme-linked immunosorbent spot (ELISPOT) to assess cellular immune responses to AAV capsid, FIX, R338L, and other peptide pools will be presented in a summary table.

Anti-Drug antibody (ADA) and neutralizing antibody (nAb) to AAV capsid results from the central lab will be collected according to the SoA.

FIX Inhibitor results by Bethesda Assay will be collected throughout the study and reported.

3.3. Other Endpoint(s)

3.3.1. Joint Assessments

Joint health will be assessed via multiple methods in this study. In general, missing data will not be imputed for joint assessment results.

3.3.1.1. Target Joints

A target joint is defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6-month period). Investigators will assess the health of the target joint(s), identified at baseline (during screening period of study C0371002) and other visits, as scheduled per SoA. A target joint is considered resolved when there are ≤2 bleeds into the joint within a 12-month period. A newly developed target joint is a major joint that is not identified as target joint at baseline, and has three or more spontaneous bleeds within a consecutive 6-month period post PF-06838435 infusion. If prophylaxis FIX regimen is resumed for a participant, then the time period following the resumption of the prophylaxis regimen will be excluded from the identification of target joints. The baseline assessment is based on the closest evaluation prior to PF-06838435 infusion, which is measured during the screening period of Study C0371002.

3.3.1.2. X-ray Assessments to Evaluate Joints

Some participants (n~40), who consent to participate in an optional substudy, will undergo X-ray assessment of knees, elbows and ankles to assess damage within joints detectable at a radiologic level. X-rays will be acquired according to the SoA. At a minimum, joint images will be reviewed following the Pettersson scale [2]. The overall score and joint level score will be calculated. If the X-ray cannot be performed during the baseline period, it is acceptable to postpone this testing to no later than the Week 4/Visit 6 and baseline will be defined as the assessments during the baseline period or at Week 4/Visit 6. If the baseline X-ray could not be performed before or at the Week 4/Visit 6, the study participant does not need to do the 3 (Visit 17) and 6-year (Visit 20) follow-up X-rays.

3.3.1.3. Magnetic Resonance Imaging (MRI) to Evaluate Joints

Some participants (n~20), who consent to participate in an optional substudy, will undergo magnetic resonance imaging (MRI) exams to assess damage within joints by evaluating soft-

tissue changes and osteochondral changes. The MRI scanning protocol will include acquisition of knees, elbows and ankles. The MRI images will be read centrally and the scores will be based on the extended MRI scale with a final score combining soft-tissue and osteochondral sub-scores to form a total score of joint image from 0-5 (0 to be the best and 5 to be the worst). MRI scans will be acquired according to the SoA. If the MRI can't be performed during the baseline period, it is acceptable to postpone this testing no later than Week 4/Visit 6. If the baseline MRI as part of a substudy could not be performed before or at Week 4/Visit 6, the study participant does not need to do the 3- (Visit 17) and 6- (Visit 20) year follow-up MRIs. Baseline is defined as the assessments during the baseline period or at Week 4/Visit 6.

3.3.2. Additional PRO Assessments

3.3.2.1. Hemophilia Life Impacts Questionnaire (HLIQ)

The Hemophilia Life Impacts Questionnaire (HLIQ) is a 9-item assessment of life impacts associated with living with and treating hemophilia. The HLIQ employs a 'past week' recall period. Four items are assessed on a 5-point, ordinal, verbal rating scale (VRS) scored from 0 to 4, while 4 items are rated such that responding 'yes' branches to a 5-point, ordinal VRS and responding 'no' branches to a reason for not participating in the activity, i.e., due to hemophilia or due to other reasons. One item is assessed on a 4-point, ordinal VRS scored from 0 to 3. Higher scores on the VRS indicate greater impact due to living with or treating hemophilia. HLIQ baseline is the closest evaluation prior to or on the day of PF-06838435 infusion, which is measured during the screening period of Study C0371002.

3.3.2.2. EQ-5D-5L

Developed by the EuroQol Group, the EuroQol, 5 dimensions, 5 levels (EQ-5D-5L) is considered the premier measure of health status used in the assessment of the Quality Adjusted Life Year (QALY). It measures 5 dimensions of health on a 5-point (5L) scale including Mobility, Self-care, Usual activities, Pain/discomfort, and Anxiety/depression. Also included is a visual analog scale (VAS) anchored by worst and best imaginable health on a 0 to 100 scale where participants are asked to indicate where on the scale, they rate their current health.

Each of the 5 dimensions (i.e., 'Mobility', 'Self-care', 'Usual activities', 'Pain/discomfort', and 'Anxiety/depression') in the EQ-5D questionnaire is assessed with 5 levels of perceived problems:

Level 1	No problem
Level 2	Slight problems
Level 3	Moderate problems
Level 4	Severe problems
Level 5	Extreme problems

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

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

The number and percentage of participants in each level of the 5 dimensions of health score will be assessed and summarized. The VAS score and the Index score (total score) at each visit will be compared with baseline. Missing data will not be imputed, which means missing individual question responses will lead to missing domain scores and total score. EQ-5D-5L baseline is the closest evaluation prior to or on the day of PF-06838435 infusion, which is measured during the screening period of Study C0371002.

3.3.3. Vector Shedding

Vector shedding of PF-06838435 in plasma, saliva, PMBC, urine, and semen will be assessed until 3 consecutive specimens reach below the limit of detection for the given specimen type. Peak value is defined for each participant as the largest result collected prior to the first set of 3 consecutive negative results. Peak values, time to peak values, and the time to 3 consecutive specimens reaching below the limit of detection for each specimen type will be summarized. For the vector shedding summaries, the date of the first set of three consecutive assessments below the limit of detection will be used as the vector clearance date. Additionally, analyses will separately consider the time to the last of the first set of three consecutive negative results, and time to the last positive prior to the first set of three consecutive negatives showing value below the limit of detection will be used as the vector clearance date. Additionally, saliva, semen, and urine samples for time points from a subset of participants will be analyzed for deoxyribonuclease (DNase)-resistant particles and will be summarized separately.

A subgroup of participants will have more extensive vector shedding analysis performed on their specimens to further characterize the kinetics of vector shedding. The data of this subgroup will be separately presented.

3.3.4. FIX Antigen Levels and Coagulation Activation Tests

FIX antigen will be assessed in parallel with FIX:C and follows the same rule that any sample taken within 7 days after(14 days if Extended half-life [EHL] product is used) of exogenous FIX replacement therapy administered for any purpose (including treatment of bleeding, preventive purpose, or resumption of FIX prophylaxis regimen) will be excluded from the analysis of FIX antigen. The assessment value of FIX antigen will be summarized.

Coagulation activation tests are: activated partial thromboplastin time (aPTT), international normalized ratio (INR), D-dimer, thrombin generation assay (TGA), thrombin-antithrombin level (TAT). The tests will be conducted at baseline, post-baseline and as clinically indicated throughout the study.

3.4. Baseline Variables and Covariates

Baseline definition for each relevant endpoint is defined in the above section, as needed.

Baseline characteristic will be summarized and will include Age group (cut-off <35, or ≥35 years), and Region (North America, Europe, Asia/Pacific, and South America).

3.5. Safety Endpoints

The safety endpoints of this study include vital signs, electrocardiogram (ECG), adverse events (AEs), serious AEs (SAEs), physical examination findings, laboratory test results, surgery information and liver ultrasound findings.

3.5.1. Adverse Events

The summary tables of AE will be based on data collection presented in Figure 2 below. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (i.e., before undergoing any study-related procedure and/or receiving PF-06838435), through and including 6 years after the last administration of the PF-06838435, or at End of Study (EOS) for participants who discontinue. The active collection period for this study is categorized into Short Term (up to and including 52 weeks post PF-06838435 infusion). The Long-Term Monitoring Period is defined as Week 53 post PF-06838435 infusion until EOS.

During the Short Term Monitoring Period, all SAEs (including medically important events (MIE), see protocol Appendix 3) and all non-serious AEs will be collected.

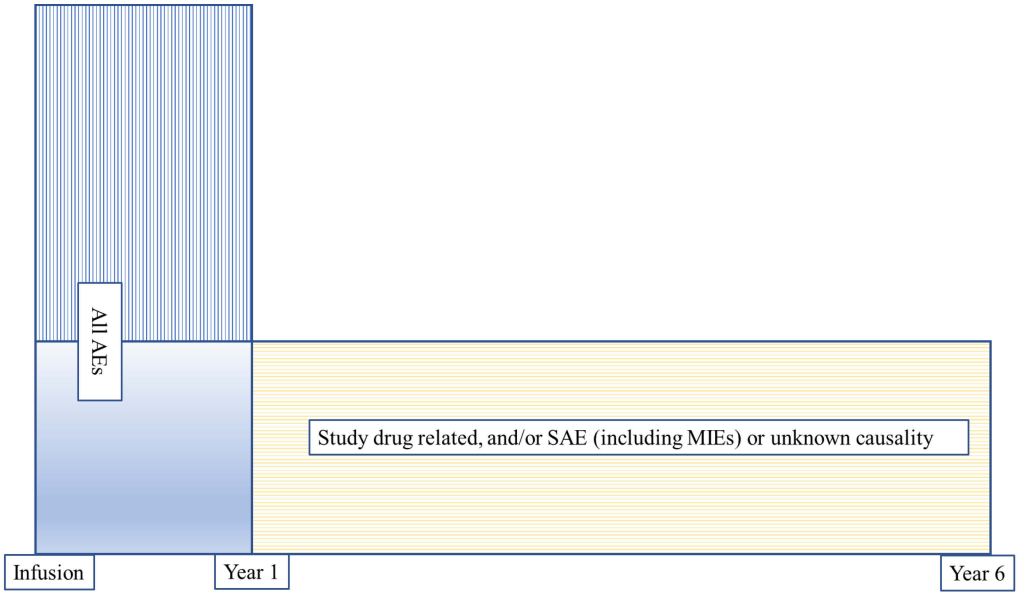
During the Long-Term Monitoring Period the following adverse events will be collected:

- SAEs (including MIEs, see protocol Appendix 3);
- Non-serious AEs determined to be related to PF-06838435 by the investigator or where causality is unknown;

Adverse Events of Special Interest (AESIs), as detailed in protocol Appendix 3, will be summarized. There is no lag time specified for adverse event reporting in this study.

Treatment emergent adverse events (TEAEs) include any adverse events that occur on or after the infusion of PF-06838435. Missing severity will be not imputed. AEs will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) available at the time of database release and summarized by system organ class and preferred term.

Figure 2. Adverse Events to be Included in the Short Term and Long-Term Summary



3.5.2. Laboratory Data

Safety laboratory data collected in this study include:

- Hematology: white blood cell (WBC) and differential, red blood cell (RBC), hemoglobin, hematocrit, and platelet count;
- ABO blood group (at Screening if unknown);
- Chemistry: Na, K, Cl, phosphate, bicarbonate, glucose, blood urea nitrogen (BUN), serum creatinine.

Certain selected lab tests will only be conducted at screening, and again if clinically indicated. For example:

- Hepatitis: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis B virus (HBV)- deoxyribonucleic acid (DNA); hepatitis C virus (HCV)- Ribonucleic acid (RNA) Quantitative, HCV viral load (if indicated);
- Liver fibrosis: FibroScan, FibroTest/FibroSURE, AST to platelet ratio index (APRI);
- human immunodeficiency virus (HIV): Antibody testing, and CD4 count/HIV viral load (if antibody positive);
- Urinalysis: pH, specific gravity, protein, blood, ketones, glucose.

Liver function tests:

Some study-specific laboratory test results, such as , α-Fetoprotein and liver function test (LFT) are to be collected. Elevations in Alanine transaminase (ALT)/ Aspartate transaminase (AST) (with associated ELISPOT data) and/or steroid therapy will be identified and reported.

The baseline assessment is based on the latest evaluation prior to or on the day of PF-06838435 infusion.

3.5.3. Vital Signs and Other Safety Endpoints

Vital signs, electrocardiograms (PR, QRS, QT, and corrected QT intervals (QTc)) measurements and abnormality, abnormal finding from physical examination will be summarized.

3.5.4. Concomitant Medication

Any concomitant therapy throughout the study will be collected as follows:

- All concomitant therapy during the Short-Term Monitoring Period (up to and including 52 weeks post PF-06838435 infusion);
- The concomitant therapy associated with adverse events (AEs) to be reported during the Long-Term Monitoring Period (Week 53 post PF-06838435 infusion until EOS).

Concomitant medication will be coded, and missing data will be handled per Pfizer data reporting standard.

3.5.5. Liver Ultrasound

All participants will undergo ultrasound imaging of the liver at times specified in the SoA.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

This study is an open-label, single-arm study. The populations for analyses are outlined in the table below.

Population	Description
Enrolled	All participants who sign the informed consent form (ICF) and meet all inclusion/exclusion criteria
Dosed	All participants enrolled in the study and who received PF-06838435 infusion
Safety	All participants enrolled in the study and who received PF-06838435 infusion, which is the same as dosed population.
Evaluable	All participants enrolled in the study and who received PF-06838435 infusion and have no significant interruption of efficacy measurement.

The Evaluable analysis population listed above would exclude participants with significant interruption of efficacy measurement, or participants who do not have or have not yet completed 15 months of follow up post PF-06838435 infusion. Significant interruption will be assessed after discussion between the investigator and the medical monitor, e.g., if a participant requires a major surgery, this will be a significant interruption of measurement.

In this study, there are also substudies planned, for which the analysis populations are outlined below.

X-ray Substudy Analysis Population	All dosed participants sign the additional ICF for the X-ray substudy and meet all inclusion/exclusion criteria, and the participant's joint images have been reviewed.
MRI Substudy Analysis Population	All dosed participants who are dosed and sign the additional ICF for the MRI substudy and meet all inclusion/exclusion criteria, and the participant's joint images have been reviewed following the extended MRI scale with a final score combining soft-tissue and osteochondral sub-scores at baseline, and any data post-baseline
Vector Shedding Substudy Analysis Population	All dosed participants who sign the additional ICF for the Vector Shedding substudy and meet all inclusion/exclusion criteria, and who have any additional vector shedding data

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis is planned when 40 participants have completed 15 months of follow up after infusion of PF-06838435. The final analysis will be conducted when all dosed participants have completed the entire study (planned 6 years in duration per participant)/or discontinued. There may be several periodic reviews of data between primary analysis and final analysis for the purpose of publications and regulatory updates, etc.

The planned primary analysis is focused on the data collected during the first 15 months post infusion of PF-06838435. Unless otherwise specified analyses will be performed on the Dosed population and will include available data from the time of infusion (or Week 12 as appropriate) through 15 months post infusion regardless of the length of follow up. The final analysis will analyze extended efficacy and longer-term safety and will be performed once all participants have been followed for 6 years or have otherwise withdrawn from study. The endpoint assessments at the specific time points are listed in the table below.

Endpoint	**Primary analysis** **Statistical Analysis**
• Primary	ABR for total bleeds (treated and untreated, from Week 12 to Month 15)
• Secondary	ABR for treated bleeds from Week 12 to Month 15 AIR for FIX infusions from Week 12 to Month 15 Actual value of FIX:C by study visit and the geometric mean of FIX:C from Week 12 to Month 15 FIX consumption, from Week 12 to Month 15 Number of bleeding events of specific type from Week 12 to Month 15: spontaneous, traumatic; and untreated bleeding. Frequency of target joint bleeds, from Week 12 to Month 15 Percentage of participants without bleeds (total bleeds and treated bleeds) will be summarized from Week 12 to Month 15. HJHS at 12 months post PF-06838435 infusion Haem-A-QoL Physical Health domain and HAL Complex Lower Extremity Activities component score at 12 months post PF-06838435 infusion

	Short-term safety
• Exploratory	Haem-A-QoL (domains not previously specified) HAL (scores not previously specified) HLIQ item scores at 12 months EQ-5D-5L index score and visual analog scale at 12 months Correlation of FIX:C between one-stage assays and chromogenic straight assay
Vector Shedding Substudy	
• Exploratory	A subset of participants will have more extensive vector shedding analysis performed on their specimens to further characterize the kinetics of vector shedding.
	Final analysis
• Secondary	ABR for total bleeds (treated and untreated) from Month 15 to Month 24, by yearly intervals after first 24 months and across 6 years of follow up Annualized bleeding rate for treated bleeds from Month 15 to Month 24, by yearly intervals after first 24 months and across 6 years of follow up Annualized infusion rate from Month 15 to Month 24, by yearly intervals after first 24 months and across 6 years of follow up Actual value of FIX:C by study visit and the geometric mean of FIX:C from Month 15 to Month 24, by yearly intervals after first 24 months and across 6 years of follow up Annualized FIX consumption from Month 15 to Month 24, by yearly after first 24 months and across 6 years of follow up Number of bleeding events of specific type from Month 15 to Month 24, by yearly intervals after first 24 months and across 6 years of follow up: spontaneous and traumatic, and untreated bleeding. Frequency of target joint bleeds from Month 15 to Month 24, by yearly after first 24 months and across 6 years of follow up HJHS yearly after first 12 months through 6 years of follow up Haem-A-QoL Physical Health domain and HAL Complex Lower Extremity Activities component score yearly after the first 12 months through 6 years of follow up Longer-term safety endpoints
• Exploratory	Haem-A-QoL (domains not previously specified) HAL (scores not previously specified) HLIQ item score yearly after the first 12 months through 6 years of follow up EQ-5D-5L index score and visual analog scale yearly after 12 months through 6 years of follow up Correlation of FIX:C between one-stage assays and chromogenic straight assay
X-ray Substudy	
• Exploratory	Joint images will be reviewed and overall score, the score at specific joint, and target joint will be derived at year 3 and after 6 years of follow up.
MRI Substudy	

• Exploratory	Joint images will be reviewed following the extended MRI scale with a final score combining soft-tissue and osteochondral sub-scores (at year 3 and after 6 years of follow up).
Vector Shedding Substudy	
• Exploratory	A subset of participants will have more extensive vector shedding analysis performed on their specimens to further characterize the kinetics of vector shedding.

5.1. Hypotheses and Decision Rules

In this study, all hypothesis testing will use a two-sided test, unless specified otherwise.

The primary objective is to demonstrate the efficacy of a single infusion of PF-06838435 in male participants ≥18 years of age with moderately severe to severe hemophilia B (FIX:C ≤2%). The primary objective is addressed via the primary endpoint of ABR_{total}.

The hypothesis test of ABR_{total} is noninferiority test of pre- and post treatment with PF-06838435 with a noninferiority margin of 3.

A gatekeeping process will be applied to control multiplicity of testing multiple endpoints at the primary analysis. The subsequent hypothesis testing will only be performed after success on a previous hypothesis test, each test performed at the α defined for the primary analysis (0.05). The analyses cease when a failure occurs. The sequence of gatekeeping process is displayed in Table 2. For the last group of hypothesis tests, we would apply Hochberg (1988) step-up procedure so that the familywise error rate will be controlled under 0.05. Note, only selected endpoints are included in the sequence in the table below.

Table 2. Sequence of Gatekeeping Process of Multiple Hypothesis Tests

Hypothesis testing ceases when a failure occurs									
ABR_{total} non-inferior to FIX prophylaxis regimen#	ABR_{treat} non-inferior to FIX prophylaxis regimen#	AIR superiority to FIX prophylaxis regimen	Steady state FIX:C >5%*	FIX consumption superiority to FIX prophylaxis regimen	ABR_{treat} superiority to FIX prophylaxis regimen	ABR_{total} superiority to FIX prophylaxis regimen	Haem-A-QoL Physical Health domain significantly improved from baseline	HAL Complex Lower extremity Activities component score significantly improved from baseline	ABR_{total} of specific type (spontaneous, trauma, untreated, in target joints,) non-inferior to FIX prophylaxis regimen, and HJHS (Hochberg step-up method)

#The upper bound of the confidence interval of the difference in ABR_{total} and ABR_{treat} between pre- and post PF-06838435 will be compared to the NI margin. All other hypothesis tests are 2-sided tests.
*Steady state FIX:C will be analyzed using a one-sided, one sample t-test.

5.2. General Methods

The efficacy of study medication is obtained via comparison of pre- and post PF-06838435 infusion measure collected for each participant. For comparisons of ABR, AIR, and FIX consumption, pre PF-06838435 data are from the Pre-Infusion Period consisting of data collected in the lead-in study C0371004 and during the period prior to study drug infusion in C0371002. For comparisons of safety evaluation and other efficacy endpoints, pre PF-06838435 data will be from baseline in C0371002, which is defined in Section 3 for each endpoint.

Visit windows may be developed for specific data points (i.e., FIX:C, ABR, AIR, annualized FIX consumption and AE) in reference of SoA, so the data may be summarized by visit. Each yearly observation period used for analysis will be 365 days, beginning with PF-06838435 infusion where days is calculated relative to the date of PF-06838435 infusion in C0371002 +1 day. Any visit dates beyond 2190 days will also be included in Year 6 for analysis.

For AE, the following visit windows will be applied:

Year	
1	Date of PF-06838435 infusion < Year 1 ≤ 365 days
2	365 days < Year 2 ≤ 730 days
3	730 days < Year 3 ≤ 1095 days
4	1095 days < Year 4 ≤ 1460 days
5	1460 days < Year 5 ≤ 1825 days
6	1825 days < Year 6

Further details of windowing will be described separately for each endpoint in Section 3, as applicable.

For ABR_{treat}, AIR, ABR_{total}, annualized FIX consumption, and ABR_{total} of specific bleed types, the primary analysis period will include all assessments from Week 12 (Day 82) to Month 15 (Day 469). And Year 2 will include all assessments from Day 470 to Day 730. Year 3 to Year 6 have the same visit windows as listed above for AE.

For FIX:C, visit window will be considered when deriving yearly intervals:

Year	
Week 12 to Month 15	82 days < Week 12 to Month 15 ≤ 469 days

2	470 days < Year 2 ≤ 744 days (Week 104+2 weeks of visit window, Day 744)
3	745 days < Year 3 ≤ 1109 days (Week 156+2 weeks of visit window, Day 1109)
4	1110 days < Year 4 ≤ 1481 days (Week 208+3 weeks of visit window, Day 1481)
5	1482 days < Year 5 ≤ 1846 days (Week 260+3 weeks of visit window, Day 1846)
6	1847 days < Year 6

For participants in whom the corticosteroid treatment are initiated, FIX:C and ABR_{total} will be calculated for the following periods:

Periods	**Derivation of time period (Corticosteroid is initiated before Week 12 [Day 82])**	**Derivation of time period (Corticosteroid is initiated after Week 12 [Day 82])**
prior to corticosteroid initiation	Not calculatable	date of corticosteroid initiation – Day 82
during corticosteroid treatment	date of stop of corticosteroid – Day 82 +1 *if corticosteroid is stopped before Day 82, then this time period will not be calculated.	date of stop of corticosteroid – date of initiation of corticosteroid +1
post-corticosteroid treatment	Month 15 or last contact date if has not reached Month 15 – date of stop of corticosteroid (or Day 82, whichever is later)	Month 15 or last contact date if has not reached Month 15 – date of stop of corticosteroid
overall time period	Month 15 (or last contact date if has not reached Month 15) – Day 82 +1	Month 15 (or last contact date if has not reached Month 15) – Day 82 +1

*days without corticosteroid treatment will be excluded from the derivation of corticosteroid treatment period.

5.2.1. Analyses for Binary Endpoints

Descriptive statistics of binary data will include the number of non-missing observations, the frequency of the observed endpoint as well as the observed proportion. The two-sided 95% CI of the observed proportion will be provided (when appropriate) using the exact method.

5.2.2. Analysis for Count Endpoints

For count variables such as ABR, AIR and bleeding episodes of specific types, the detailed analysis method will be discussed in Section 6. The median, the mean, interquartile range, minimum and maximum of the observed data will be reported in summary tables.

5.2.3. Analyses for Continuous Endpoints

The median, first quartile (Q1), third quartile (Q3), minimum, maximum, mean, standard deviation, 95% confidence interval (CI) of the observed value and the change from baseline, where appropriate, will be summarized in the tables.

5.2.4. Analyses for Categorical Endpoints

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

5.3. Methods to Manage Missing Data

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

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. ABR for Total Bleeds

6.1.1.1. Main Analysis

ABR_{total} will be analyzed using a repeated measures generalized linear model with negative binomial distribution and identity link function. Treatment (prophylaxis, or PF-06838435) and duration will be included in the model. Treatment will be a class factor in the model, duration is numeric and participant will be a random effect. Duration is the elapsed time in years of each treatment period. Duration is at least 0.5 for pre-PF-06838435 infusion prophylaxis which corresponds to six months. This period begins at enrollment of the lead-in study and ends on date of PF-06838435 infusion. Duration of PF-06838435 period is the observed time from Week 12 (Day 82) until cutoff for the specified analysis (e.g. 15 months for the primary analysis) or the date of study withdrawal or resumption of FIX infusion (whichever is earlier), minus any time that is predefined to be excluded.

- The Dosed population will be the primary analysis population. Analysis will be repeated for the Evaluable population if it is different from Dosed population.

- The mean ABR_{total} from Week 12 to Month 15 will be compared to the pre-infusion mean via the estimation of the mean difference and 95% CI. If the upper bound of the confidence interval of the difference of (ABR_{total} PF-06838435 – ABR_{total} FIX prophylaxis) is smaller than 3.0, then statistical significance of the noninferiority claim would be demonstrated. An example of SAS code of such analysis is included in the Appendix 1.1. If noninferiority is demonstrated, further testing for superiority would be conducted after the primary analysis (assuming other endpoints within the

testing hierarchy are statistically significant), using the same method, except the margin would be modified to 0.

- The summary table will include two columns, for FIX prophylaxis and PF-06838435, respectively. The summary statistics in the table will include n, mean, median, Q1, Q3, range of the observed ABR_{total}, model derived mean ABR_{total} and 95% CI, estimated mean difference (model derived), and the 95% CI of the mean difference (model derived).

6.1.1.2. Supplementary Analysis

As a supportive analysis, the frequency of bleeding will also be analyzed using a repeated measures generalized linear model with negative binomial distribution and log link function. Treatment (prophylaxis, or PF-06838435) will be a class factor in the model, and participant will be a random effect. Log transformed duration of time on study will be included as an offset variable in the model. Mean percentage of reduction in ABR_{total} and its 95% CI, as well as p-value will be provided. Sample SAS code is provided in Appendix 1.2.

The following sensitivity analyses will be performed:

1. Comparing the ABR_{total} from Week 12 to Month 15 to the ABR_{total} collected during C0371004 , excluding pre-infusion bleeds from C0371002.
2. Comparing the ABR_{total} from Week 12 to Month 15 to the ABR_{total} during the most recent 6 months prior to infusion.
3. A "Jump to Reference" analysis will be performed to assess the impact on ABR_{total} of participants who discontinue the study prior to completing follow up (including those with FIX infusion resumption). The ABR_{total} for participants who were dosed at least 15 months prior to the data cutoff date but discontinued prior to completing 15 months of follow up will be included in the analysis with the ABR_{total} during the time period between discontinuation and Month 15 imputed based on the ABR on prior prophylaxis.
4. Sensitivity analysis on ABR_{total} of first 15 months post PF-06838435 infusion will be conducted.

These sensitivity analyses will be conducted on the Dosed population.

ABR_{total} Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5, and Year 6, as well as ABR_{total} through the overall follow up will be compared to ABR_{total} of FIX prophylaxis using the same statistical methods as ABR_{total} is analyzed, first to assess noninferiority with noninferiority margin 3 and then to assess superiority if noninferiority is established.

A table will be provided summarizing ABR_{total} during the following periods: prior to corticosteroid initiation, during corticosteroid treatment and post-corticosteroid treatment (Section 1.1.1) for the participants in whom corticosteroid is initiated. ABR_{total} during the overall time period (Week 12 to Month 15) for participants who do not have corticosteroid treatment will be presented side by side in the same table.

The above analysis will be conducted on Dosed population.

6.2. Secondary Endpoint(s)

6.2.1. ABR for Treated Bleeds

ABR_{treat} from Week 12 to Month 15, one of the key secondary endpoints, will be compared to ABR_{treat} of FIX prophylaxis using the same statistical methods as ABR_{total} is analyzed. If noninferiority is demonstrated, further testing for superiority would be conducted. Analysis will be done on Dosed population and repeated in Evaluable population if it is different from Dosed population.

Three sensitivity analyses will be performed on Dosed population:

1. Comparing the ABR_{treat} from Week 12 to Month 15 to the ABR_{treat} collected during C0371004, excluding pre-infusion bleeds from C0371002.
2. Comparing the ABR_{treat} from Week 12 to Month 15 to the ABR_{treat} during the most recent 6 months prior to infusion.
3. ABR_{treat} during first 15 months post PF-06388435 infusion will be analyzed similarly as ABR_{treat} from Week 12 to Month 15.

ABR_{treat} Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5, and Year 6, as well as ABR_{treat} through the overall follow up will be analyzed similarly as ABR_{treat} from Week 12 to Month 15 using Dosed population.

6.2.2. AIR

6.2.2.1. Main Analysis

AIR is one of the key secondary endpoints. AIR for FIX from Week 12 to Month 15 vs AIR during SOC FIX replacement regimen will be tested for superiority to demonstrate the reduction of overall burden to moderately severe and severe hemophilia B participants.

- The Dosed population will be the primary analysis population. Analysis will also be done on Evaluable population if it is different from Dosed population.

- The AIR will be compared to AIR of FIX prophylaxis regimen using paired t-test. The summary table will include two columns, for FIX prophylaxis and PF-06838435, respectively. The summary statistics in the table will include n, mean, median, Q1, Q3, range of the observed AIR, estimated mean difference, the 95% of CI of the mean difference, the upper bound of the CI of (AIR PF-06838435 – AIR FIX prophylaxis) with the proper α will be presented in the summary table. Mean percentage of reduction and 95% CI using t distribution will also be presented, where percentage of reduction is defined as (1- mean AIR for FIX from Week 12 to Month 15 /mean AIR during SOC FIX replacement regimen) x 100%.

6.2.2.2. Sensitivity/Supplementary Analysis

Percentage of the participants without exogenous FIX infusions will be defined in the overall time period after PF-06838435 infusion, the running total time period (i.e., Week 12 to Month 15, Week 12 to Year 2, Week 12 to Year 3, etc.) and with the same time periods as ABR such as Month 15, Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5 and Year 6. Descriptive statistics will include the total number of participants, frequencies and percentages of participants who have/have no infusions. The Dosed population will be used for this analysis.

Three sensitivity analyses will be performed:

1. comparing the AIR from Week 12 to Month 15 to the AIR collected during C0371004

2. comparing to the AIR during the most recent 6 months prior to infusion.

3. AIR during first 15 months post PF-06388435 infusion will be analyzed similarly as AIR from Week 12 to Month 15.

These analyses will be conducted on Dosed population.

The percentage of the participants who resume a FIX prophylaxis regimen will be determined for the overall time period, as well as for each time interval (from Week 12 to Month 15, Month 15 to Month 24, Year 3, Year 4, Year 5 and Year 6).

If there are a sufficient number (i.e., >20%, which is around 8 at the time of the final analysis) of participants who resume a FIX prophylaxis regimen, then the time to resumption of a prophylaxis regimen will be summarized.

AIR Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5 and Year 6, as well as AIR through the overall follow up will be tested using the same method to demonstrate superiority over AIR of SOC FIX prophylaxis regimen as secondary endpoints.

6.2.3. FIX:C

6.2.3.1. Main Analysis

A log transformation of the steady state FIX:C (as the endpoint defined in Section 3, the geometric mean is the antilog of the mean of the log-transformed values) will be compared to a threshold of log(5) using a one-sided, one-sample t-test.

- The Dosed population will be the primary analysis population. Analysis will also be done on the Evaluable population if it is different from Dosed population.

- The sample size, mean and t-based 95% CI, standard deviation, median, Q1, Q3, minimum, and maximum of FIX:C (all descriptive statistics will be transformed back to original scale) will be presented in the summary tables. For the primary analysis,

assessments with missing data imputation will be utilized. Another supportive analysis will also be conducted with only observed data.

6.2.3.2. Sensitivity/Supplementary Analyses

Similar analyses comparing the FIX:C Year 2 to 6 to the threshold of 5% will be conducted. The window for Year 2 will be from Month 15 through Month 24 as previously described. The above analysis will be conducted on Dosed population.

Similar summaries will also be provided for FIX:C during the following periods: prior to corticosteroid initiation, during corticosteroid treatment and post-corticosteroid treatment (Section 5.2) for the participants in whom corticosteroid is initiated. FIX:C during the overall time period (Week 12 to Month 15) for participants who do not have corticosteroid treatment will be presented side by side in the same table.

An individual plot will be generated to visualize FIX:C values of the Dosed population. The graph will display all FIX:C measurements excluding the ones within the window of FIX infusion.

Actual value of FIX:C will be presented in a summary table by study visit with mean, SD, 95% CI of the mean, median, min, max, Q1 and Q3. A box-whisker plot will also be provided for data visualization purpose. In addition, a stacked bar graph will be generated by study visit, presenting percentage of participants falling into the following category (FIX:C: 0-<5%, 5-<15%, 15-<50%, 50-<150%, ≥150%). If a participant withdrew consent, dropped out early from the study or resumed FIX prophylaxis, then the missing assessment will be imputed as 1.9%. For the primary analysis, assessments with missing data imputation will be utilized for summaries. Another supportive analysis will also be conducted with only observed data.

The FIX:C results by two different one-stage assays along with analysis by chromogenic assay will be visualized in graphs with chromogenic value on the x-axis and both one-stage assay results on the y-axis. The FIX:C results of two-stage assays will be visualized using scatter plot.

The Pearson's correlation will be calculated for each pair of the three assays.

6.2.4. Annualized FIX Consumption

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

6.2.5. Annualized Bleeding Rate of Specific Type

The ABR_{total} of specific types such as spontaneous bleeding, traumatic bleeding, bleeding in joints, bleeding in soft tissue, and untreated bleeding etc. These endpoints will be analyzed similarly as defined for main analysis of ABR_{total}.

These analyses will be conducted on Dosed population.

6.2.6. Percentage of Participants without Bleeding

Percentage of the participants without treated bleeding will be defined in the overall time period after PF-06838435 infusion, the running total time period (i.e., Week 12- Month 15, Week 12-Year 2, Week 12- Year 3, etc.) and with the same time periods as ABR such as Week 12 to Month 15, Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5 and Year 6.

The percentage of participants without any bleeding (including treated and untreated) will be defined as well in the overall time period after PF-06838435 infusion, the running total time period (i.e., Week 12- Month 15, Week 12-Year 2, Week 12- Year 3, etc.) and with the same time periods as ABR such as Week 12 to Month 15, Year 2 (Month 15 to Month 24), Year 3, Year 4, Year 5 and Year 6.

Descriptive statistics will include the number of participants, frequencies, and the percentage of participants who have/have no bleeding. The Dosed population will be used for this analysis.

6.2.7. Hemophilia Joint Health Score (HJHS)

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

The n, median, mean and standard deviation, the 95% confidence limits of actual value and the change from baseline will be reported in the summary table. The Dosed population will be used for this analysis.

The HJHS value at different visits will be analyzed in a longitudinal model as exploratory analysis to study the trend of the HJHS using MMRM model with participant as random factor, and years since infusion as the continuous variable. The Dosed population will be used for this analysis.

6.2.8. Patient-Reported Outcomes

Patient Global Impression of Change – Hemophilia (PGIC-H) will enable an anchor-based method approach for evaluating the meaningful within-patient change (MW-PC) for Haem-A-QoL, HAL and HLIQ (described in Section 6.3.2). The details about anchor analysis will be provided in a separate PRO SAP and thus not described in detail here.

6.2.8.1. Haem-A-QoL

The 10 domains of health-related quality of life as well as the total score will be calculated, and each compared to its own baseline using paired t-test. The Physical Health domain will be the main endpoint of this instrument. The n, median, mean and standard deviation, the 95% confidence limits of actual value and the change from baseline will be summarized by visit in the table. The Dosed population will be used for this analysis.

6.2.8.2. Hemophilia Activities List (HAL, v2)

The 7 domains of the HAL and three component scores can be calculated and will each be compared to its own baseline using paired t-test. Complex activities involving the Lower Extremities will be main endpoint for this instrument. The n, median, Q1, Q3, minimum, maximum, mean and standard deviation, the 95% confidence limits of actual value and the change from baseline will be reported by visit in the summary table. The Dosed population will be used for this analysis.

6.2.9. Immunogenicity

Percentage of participants with positive/negative IFNγ to each pool, FIX overall and capsid overall will be summarized by the specified sampling timepoint for participants in whom the corticosteroid treatment is initiated.

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

Descriptive summaries will be provided for ADA by study week. Number and percentage of participants with positive ADA will also be summarized by study week. Unscheduled assessments will also be presented. Data will also be presented in a listing. Two scatter plots will be generated, plotting steady state FIX:C against ADA titer at Screening visit and ADA titer at Week 52, respectively.

Number and percentage of participants with FIX inhibitor by the Bethesda Assay post PF-06838435 infusion will be summarized.

6.3. Other Endpoint(s)

6.3.1. Joint Assessments

6.3.1.1. Target Joints

Number and percentage of participants with 0, 1, 2 or ≥3 target joints at baseline, during the first 15 months post PF-06838435 infusion, and during the overall follow-up period will be summarized, respectively. Number and percentage of participants who have 0, 1, 2 or ≥3 baseline target joints resolved during the first 15 months post PF-06838435 infusion, and during the overall follow-up period will be summarized. Similarly, number and percentage of participants who developed new target joints (1, 2 or ≥3 target joints) during the first 15 months post PF-06838435 infusion, and during the overall follow-up period will be summarized. The number and location of target joints at baseline and post PF-06838435 infusion will be provided in a data listing.

The Dosed population will be used for this analysis.

6.3.1.2. X-ray Assessments to Evaluate Joints

The overall score, the score at specific joint, and target joint, as well as the change from baseline will be summarized by study visit. The assessment values will be compared to baseline using paired t-test. The summary table will include two columns, for FIX prophylaxis and PF-06838435, respectively. The n, median, Q1, Q3, minimum, maximum, mean and standard deviation, the 95% confidence limits of actual value and the change from baseline will be reported in the summary table. The "X-ray substudy" population will be used for this analysis.

6.3.1.3. Magnetic Resonance Imaging (MRI) to Evaluate Joints

Final score combining soft-tissue and osteochondral sub-scores would be assessed to form a total score of joint image from 0-5 (0 to be the best and 5 to be the worst) will be compared to baseline using paired t-test. The summary table will include two columns, for FIX prophylaxis and PF-06838435, respectively. The n, median, Q1, Q3, minimum, maximum, mean and standard deviation, the 95% confidence limits of the actual value and the change from baseline will be reported in the summary table. The 'MRI substudy' population will be used for this analysis.

6.3.2. Additional Patient-Reported Outcomes

All PRO endpoints will be analyzed as continuous variables, each patient's post PF-06838435 infusion value will be compared to its own baseline using paired t-test to test whether the difference from baseline is greater than '0'. PGIC-H will enable an anchor-based methodology approach for evaluating the MW-PC. The details about anchor analysis will be provided in a separate PRO SAP and thus not described here.

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

PGIC-H response will be summarized as categorical variable. The response scale is a 7-point categorical response centered on 'no change' with 3 grades of improvement and 3 grades of worsening. If the number is too small for a category, the response to PGIC-H 'greatly improved' and 'moderately improved' will be combined into a category of 'at least moderately improved'. And the response of PGIC-H 'greatly worsened' and 'moderately worsened' will be combined into a category of 'at least moderately worsened'. In the summary table, the number of total non-missing observations, and frequencies, the proportion of participants in each of response category will be presented by study visit. The Dosed population will be used for this analysis.

6.3.2.2. Hemophilia Life Impacts Questionnaire (HLIQ)

The HLIQ is a 9-item assessment of life impacts associated with living with and treating hemophilia. Number and percentage of participants within each response category will be summarized for each question by study visit. The Dosed population will be used for this analysis.

6.3.2.3. EQ-5D-5L

The number and percentage of participants in each level of the 5 dimensions of health score will be assessed and summarized by visit. The VAS score and the Index score (total score) will be compared to its own baseline using paired t-test. The n, median, Q1, Q3, minimum, maximum, mean and standard deviation, the 95% confidence limits of actual value and the change from baseline will be summarized in the table. The Dosed population will be used for this analysis.

6.3.3. Vector Shedding

Descriptive summaries of shedding vector levels in PBMC, saliva, urine, semen and plasma will be provided, including a summary of peak levels and time to peak levels. If multiple assessments are collected for a study visit, the largest value will be included in the summary as a conservative approach. Number and percentage of participants with BLoQ value at each visit will also be summarized in the table. A mean ± standard error plot of vector shedding over time will be generated with specimen types differentiated by different color/symbols. In the descriptive summary table and the Mean ± SE plot, only values with assessments above LLQ will be included. In these tables and figures, results from samples without DNase treatment will be presented. The figures will be presented in log-linear scales.

For a subset of participants in C0371002, samples will also be assessed by DNase digestion method for saliva, semen and urine. For these samples, results from both Dnase-digested and DNase undigested samples will be summarized separately in another table, with columns representing the lab method. Individual plots of vector shedding over time will be generated for all participants in the Dosed population. The plot will be paged by participant and paneled by specimen type, and results from both lab methods will be plotted on the same figure, differentiated by color/symbols. In the individual plot, BLoQ value will be imputed as one half of the LLQ value for plotting purposes. Results from the two methods will be presented side by side in a data listing.

Time to undetectable vector (defined as time to first of three consecutive negative results), time to last of three consecutive negative results, and time to the last positive prior to three consecutive negative will be summarized. The summary table will be generated for the 'Vector Shedding substudy' population and the Dosed population.

Vector Shedding subgroup will have more extensive vector shedding analysis performed on their specimens to further characterize the kinetics of vector shedding. The data of this subgroup will be separately presented.

6.3.4. FIX Antigen Levels and Coagulation Activation Tests

The n, mean, median, Q1, Q3 and range will be presented in the summary tables for FIX antigen levels and coagulation activation tests as specified in Section 3.3.4.

6.4. Subset Analyses

No subset analysis is planned for this study.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

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

6.5.2. Study Conduct and Subject Disposition

Participant disposition will be summarized for the Enrolled population. This table will present the count and percentage of participants in each disposition category: number discontinued and reason for discontinuation (including number of screen failure), number completed, and number ongoing. A data listing will be provided along the disposition table.

6.5.3. Study Treatment Exposure

PF-06838435 infusion information will be summarized in the Dosed population. Duration of infusion, and total dose of PF-06838435 (in vector genomes [vg] and vector genomes per kilogram [vg/kg]), whether actual dose was adjusted from planned will be summarized.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant medication other than FIX replacement infusions and non-drug treatment will be summarized. Concomitant medication associated with AE will be summarized since these concomitant medications will be collected from Year 2 through Year 6.

6.6. Safety Summaries and Analyses

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

6.6.1. Adverse Events

An overall table summarizing AEs reported during the entire study will be sorted by system organ class and preferred term. Per protocol, adverse events assessed as non-serious and unrelated to study drug are reported within the first year post infusion only and not subject to reporting thereafter. As a consequence, the all-causality TEAE tables will include a footnote to convey non-serious unrelated AE were collected over the initial year and not the subsequent 5-year study duration for a given participant.

All AEs occurring during the first year (up to and including 52 weeks post PF-06838435 infusion) will be summarized, sorted by system organ class and preferred term. All AE summary tables will be generated to display all AEs, relationship to study drug, severity of the AE ('Mild', 'Moderate', and 'Severe'), and if serious AE or not.

All serious AEs, treatment-related non-serious AEs, AESIs, AE leading to study discontinuation, and AE leading to death will be summarized per Pfizer Data Reporting Standard, for AE reported during short term (up to and 52 weeks post PF-06838435 infusion)

and AE reported during the entire course of study including long-term monitoring (post PF-06838435 infusion to Year 6 or EOS), respectively.

6.6.2. Laboratory Data

Safety laboratory tests and other laboratory tests specified in Section 3.5.2 will be summarized descriptively by study visits.

Categorical shift of abnormal to normal, or normal to abnormal, of selected lab tests will be summarized. These lab tests are LFT, α-Fetoprotein, hematology, and clinical chemistry parameters.

LFT measures consist of protocol-specified tests, including AST, ALT, Gamma-glutamyl transpeptidase (GGT) and Lactate dehydrogenase (LDH) etc.. Baseline and post-baseline visits will be summarized with descriptive statistics by visit and will be presented in a data listing. Number of participants (n), mean, standard deviation (SD), median, Q1, Q3, minimum and maximum will be presented for all change from baseline tables. Each participant's laboratory values will be classified according to whether the test result is "low" (i.e., below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (i.e., above the upper limit of normal [ULN]). The abnormality categorical data will be summarized in shift tables comparing the results at the end of study visit, minimum post-baseline, and maximum post-baseline with those at the baseline visit.

The number and percentage of participants with corticosteroid treatment, with corticosteroid dose escalation before weaning, with corticosteroid dose escalation during weaning will be provided in addition to a summary of time to corticosteroid initiation, time from corticosteroid initiation to first wean of corticosteroid, time from corticosteroid initiation to first corticosteroid escalation, total dose and total time on corticosteroid. Total time on corticosteroid is calculated as (date of stopping of corticosteroid– date of initiation of corticosteroid +1) excluding any days without corticosteroid treatment. For summaries of corticosteroid dose escalation and dose escalation during weaning, the denominator will be the number of participants with corticosteroid treatment.

6.6.3. Vital Signs/Physical Examination/Other Safety Outcome

Vital signs, electrocardiograms, and physical examination will be summarized per Pfizer Data Reporting Standard. Any abnormal findings from liver ultrasound will be listed.

6.7. COVID-19 Related Data Listings and Summaries

The impact of Coronavirus disease 2019 (COVID-19) on C0371002 is expected to be minimal. While there was a pause in dosing new participants, since no more than the single dose of PF-06838435 infusion on Day 1 will be administered during the study, there should be no treatment discontinuations. Additionally given the mechanism of data collection for key endpoints (i.e. eDiary to capture bleeding and infusion information and the availability of mobile phlebotomy/home health services to collect blood samples) missing data due to COVID-19 is expected to be minimal for the primary endpoint (ABR_{total}) and the key

secondary endpoints (AIR, ABR_{treat} and FIX:C). Additionally, it is not anticipated that participants would discontinue from the study due to COVID-19. To confirm that COVID-19 has not impacted the trial, the following data listings and summaries will be provided.

- Study disruption/discontinuation due to COVID-19 will be listed, and a description of how the individual's participation was altered will be provided.
- Protocol Deviations related to COVID-19 will be listed.
- Missed Visits/Data for FIX:C due to COVID-19 will be listed.
- COVID-19 related Adverse Events will be summarized by system organ class and preferred term, and will also be listed.
- Any study discontinuation due to COVID-19 related AE, SAE or death related to COVID-19 will be listed.

7. INTERIM ANALYSES

7.1. Introduction

There is no interim analysis planned for this study. As this study is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment.

8. APPENDIX

Appendix 1. Statistical Methodology Details

Appendix 1.1. Example of SAS Code of Repeated Measure Additive Negative Binomial Regression Model:

```
proc genmod data=alldata;

class trt subjid;

model bleeds = years years*trt/link=identity dist=negbin noint;

repeated subject=subjid/Type=UN;

estimate ‘diff’ years*trt 1 -1/alpha=0.05; * adjust the alpha to a level if needed.

Estimate ‘Prophy’ years 1 years*trt 0 1;

estimate ‘GTx’ years 1 years*trt 1 0;

run;
```

Appendix 1.2. Example of SAS Code of Repeated Measure Negative Binomial Regression Model with log link:

```
proc genmod data=allbdyr;  (offset=natural log of years)
    class trt subjid;
    model bleeds = trt /offset=lyears dist=negbin link=log alpha=0.05; * adjust the alpha to a
level if needed.

    Repeated subject=subjid/ Type=UN;
    estimate ‘log diff’ trt 1 -1 / exp;
    ods output estimate=ci_ratio;

run;

data ci_reduction;

      set ci_ratio;

      where  Label= “Exp(log diff)” ;

Percent_reduction = 1- LbetaEstimate ;
Lower_bound = 1- LbetaUpperCL;
Upper_bound = 1- LbetaLowerCL;
Run;
```

Appendix 2. List of Abbreviations

Abbreviation	Term
AAV	Adeno-associated virus
ABR	annualized bleeding rate
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AIR	annualized (FIX) infusion rate
ALT	alanine transaminase
APRI	AST to platelet ratio index
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BLoQ	Below limit of quantification
BUN	blood urea nitrogen
CDF	cumulative distribution functions
CI	confidence interval
COVID-19	Coronavirus disease 2019
CRF	case report form
CSR	clinical study report
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
ECG	electrocardiography
EHL	extended half-life
ELISPOT	enzyme-linked immunosorbent spot
EOS	end of study
EQ-5D-5L	EuroQoL, 5-dimensions, 5-levels
FIX	Factor IX
FIX:C	Factor IX: circulating
GGT	gamma-glutamyl transpeptidase
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
hFIX-Padua	human factor IX-Padua
HIV	human immunodeficiency virus
HJHS	Hemophilia Joint Health Score
HLIQ	Hemophilia Life Impacts Questionnaire
IA	interim analysis
ICF	informed consent Form
IFNγ	interferon gamma

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IU/dL	international units per deciliter
IU/kg	International units per kilogram
IV	intravenous
LFT	liver function tests
LLN	lower limit of normal
LLQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MIE	medically important events
MMRM	mixed-effects model with repeated measures
MRI	magnetic resonance imaging
MW-PC	meaningful within-patient change
N/A	not applicable
nAb	neutralizing antibody
NI	noninferiority
PGIC-H	Patient Global Impression of Change - Hemophilia
PBMC	peripheral blood mononuclear cell
PRO	patient-reported outcome
qPCR	quantitative polymerase chain reaction
Q1	1st quartile
Q3	3rd quartile
QALY	quality adjusted life year
QTc	corrected QT
RBC	red blood cells
RNA	Ribonucleic acid
SoA	Schedule of Activities
SOC	Standard of care
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
TAT	thrombin antithrombin
TEAE	treatment emergent adverse event
TGA	thrombin generation assay
ULN	upper limit of normal
VAS	visual analog scale
vg	vector genomes
vg/kg	vector genomes per kilogram
VRS	verbal rating scale
WBC	white blood cells

9. REFERENCES

[1] F. S. B. B. e. a. Feldman BM, "Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of hte hemophilia joint health score.," vol. 63, no. 2, 2011.

[2] A. A. N. I. Pettersson H, "A radiologic classification of hemophilic arthropathy.," *Clin Orthop Relat Res,* pp. (149): 153-9, 1980.

[3] K. Lan and D. DeMets, "Discrete sequential boundaries for clinical trials.," *Biometrika,* pp. 70: 659-663, 1983.