AN OPEN-LABEL, NON-INVESTIGATIONAL PRODUCT, MULTI-CENTER, LEAD-IN STUDY TO EVALUATE PROSPECTIVE EFFICACY AND SELECTED SAFETY DATA OF CURRENT FACTOR IX (FIX) OR FACTOR VIII (FVIII) PROPHYLAXIS REPLACEMENT THERAPY IN THE USUAL CARE SETTING OF MODERATELY SEVERE TO SEVERE ADULT HEMOPHILIA B PARTICIPANTS (FIX:C≤2%) WHO ARE NEGATIVE FOR NEUTRALIZING ANTIBODIES TO ADENO-ASSOCIATED VIRUS VECTOR-SPARK100 (BENEGENE-1) AND MODERATELY SEVERE TO SEVERE HEMOPHILIA A ADULT PARTICIPANTS (FVIII:C≤1%) WHO ARE NEGATIVE FOR NEUTRALIZING ANTIBODIES TO ADENO-ASSOCIATED VIRUS VECTOR 6 (AAV6), PRIOR TO THE RESPECTIVE THERAPEUTIC PHASE 3 GENE THERAPY STUDIES

Investigational Product Number:	Not Applicable (N/A)
Investigational Product Name:	Not Applicable (N/A)
United States (US) Investigational New Drug (IND) Number:	017250; 016437
European Clinical Trials Database (EudraCT) Number:	2017-001271-23
Protocol Number:	C0371004
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 7	17 May 2022	The United Kingdom Ethics Committee requested the removal of the phrase "legally authorized representative" to avoid potentially misleading statements about participant's individual capacity to consent to the study (Schedule of Activities [footnote b], and Section 4.1, Inclusion Criterion #1 for both the Hemophilia A Population and Hemophilia B Population). Clarified that participant with a history of a neoplasm (including hepatic malignancy) that required treatment (eg, chemotherapy, radiotherapy, immunotherapy), is excluded, except for adequately treated basal or squamous cell carcinoma of the skin or a surgically removed benign neoplasm not requiring chemotherapy, radiotherapy and/or immunotherapy. Any other neoplasm that has been cured by resection should be discussed between the investigator and sponsor (Section 4.2, Exclusion Criterion #8). Increased sample size for hemophilia A participant cohort (from 70 to approximately 80 participants) to support the subsequent Phase 3 registration study, C3731003 (Section 9.1). The following changes were made to align with a PACL dated 19 October 2021: Clarified that participants with conditions associated with increased thromboembolic risk such as known inherited or acquired thrombophilia, or a history of thrombotic events, including venous thromboembolism, should be excluded so that it is not open to investigator discretion (Section 4.2, Exclusion Criterion #7).

Document	Version Date	Summary of Changes and Rationale
		Clarified which medications are permitted and medically necessary and according to standard of care (Section 5.4).
Amendment 6	23 April 2021	Clarified that, for eligibility for this study (C0371004), participation in other studies is prohibited only if it involves administration of investigational product within the last 3 months prior to study entry and/or during Study C0371002 or C3731003 participation (Section 4.2: Exclusion Criterion #9). This allows participants to have their eligibility for the subsequent treatment protocols confirmed earlier. Clarified that concomitant use of another investigational product is not permitted during study participation for consistency with clarification to Exclusion Criterion #9 (Section 5.4). Clarified the duration of follow-up for participants to allow for flexibility of enrollment into the subsequent treatment protocols (Schedule of Activities and Sections 3, 6.3, and 6.5). Expanded the sample size for hemophilia B participants to account for those who do not need to be followed for at least 6 months in this study (Section 9.1). Clarified that the participant OR a legally authorized representative may obtain consent as per local regulations (Section 4.1: Inclusion Criterion #1). Removed the option of remote screening visits and home health care services implemented via Amendment 5 since processes are not in place to support remote informed consent of participants (Schedule of Activities and Sections 6, 6.1, and 6.2).

Document	Version Date	Summary of Changes and Rationale
		Incorporated administrative changes from the 2 previous protocol administrative change letters (PACLs) dated 12 November 2020 (Sections 4.4 and 12.3) and 29 January 2021 (Appendix 4). Other minor typographical/editorial changes were made.
Amendment 5	01 October 2020	Increased sample size for participants with hemophilia B to support an additional cohort planned for the subsequent Phase 3 registration study, added clarifications on the duration of follow-up for individual participants to provide flexibility for participants who are enrolled beyond the minimum threshold of treated participants in the treatment protocols, included the option of remote screening and baseline visits to de-centralize the study visits if permitted by local regulations, removed the physical examination at the screening visit to facilitate the option of remote visits, incorporated administrative changes from the 5 previous PACLs, and removed AST-to-Platelet Ratio Index as an option for liver fibrosis testing as it is the least rigorous of the other liver fibrosis tests (FibroScan OR FibroTest/FibroSURE).
Amendment 4	12 May 2020	A country-specific requirements appendix (Appendix 4) was added for Turkey as per Turkey MoH requirement that the reference to subsequent Phase 3 studies not be included in the protocol title, as this is out of the scope of the observational study objectives defined in the Turkish regulatory guideline.
Amendment 3	27 June 2019	Including an additional cohort (hemophilia A population) as part of the 6-month lead-in study, to support the initiation of the hemophilia A gene therapy Phase 3 study. Incorporate administrative changes from the 6 previous PACLs.

Document	Version Date	Summary of Changes and Rationale
Amendment 2	07 March 2019	The United Kingdom and Ireland Ethics Committees are both mandating removal of pregnancy language from the protocol and corresponding ICD, despite sponsor providing a rationale for keeping the pregnancy language in the protocol and ICD. The Ethics Committees consider pregnancy reporting or follow-up as having no relevance to the study since this is a lead-in study and there is no exposure to investigational product.
Amendment 1	23 August 2018	Per Health Canada (HC) reporting requirements for non-investigational studies with marketed products, unusual failure in efficacy associated with the FIX replacement product in Canadian participants is reportable. This is a unique requirement to Health Canada. A country specific amendment for Canada will ensure reporting of any Lack of Efficacy (LOE) in Canadian participants to the Pfizer Drug Safety Unit (DSU) and from there to HC (for BeneFIX) or the MAH (for products other than BeneFIX) as required).
Original protocol	23 March 2018	Not applicable (N/A)

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

Amendment 8 (31 March 2023)

Overall Rationale for the Amendment: The main reason for Amendment 8 is to increase Hemophilia A cohort sample size from 80 to 95 to account for the higher than expected attrition rate following the temporary pause in the subsequent Phase 3 study (C3731003)

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Update the sample size from 80 to 95 Hemophilia A participants.	To account for higher than-expected attrition rate following the temporary pause in the subsequent Phase 3 study (C3731003).	Section 9.1 Sample Size Determination

Description of Change	Brief Rationale	Section # and Name
Non-substantial Modification(s)		
Revised the following text to inclusion criterion 5 "Participants must be on a stable FVIII prophylaxis replacement therapy (recombinant, plasma derived or extended half life FVIII product) at study entry and must have the intention to remain on FVIII prophylaxis replacement therapy for the duration of the study. This does not include nonfactor treatments (eg. Emicizumab), which are prohibited, see Section 5.4"	To clarify that non-factor treatments are prohibited. To clarify that participants must be on a stable prophylactic FVIII product regimen when entering the study; this does not include nonfactor treatments.	Section 4.1 Inclusion Criteria
Added the words "median stiffness" to exclusion criterion 5 fibroscan score.	To clarify that Fibroscan score corresponds to median stiffness.	Section 4.2 Exclusion Criteria
Added new exclusion criterion 11.	To clarify which therapies are prohibited for use during the study.	Section 4.2 Exclusion Criteria
Added the following new text to Disallowed Therapy Section "Bypassing agents (eg, factor VIIa, activated prothrombin complex concentrate) and nonfactor treatment (eg, emicizumab), except in situations where it is medically necessitated." Added the following new text to Disallowed Therapy Section "Antifibrinolytics (e.g. tranexamic acid, aminocaproic acid), except where medically indicated."	To clarify certain therapies are prohibited for use during the study and this includes bypassing agents, non-factor treatment and antifibrinolytics.	Section 5.4 Concomitant Treatment(s)/Disallowed Therapy
Added a new sentence "The reasons for preventative FIX/FVIII replacement	To clarify that the reasons for preventative infusions will now be captured and this will be done in eCRF.	Section SOA footnote g; Section 6.2 Baseline Visit; Section 6.3 Data Collection

Description of Change	Brief Rationale	Section # and Name
therapy will be captured in eCRF."		Section 6.5 End of Study/Early Termination
Reworded text to clarify what AE events are reported on the CRF and SAE form within the table under AE reporting requirement section.	To clarify what events need to be recorded on CRF as well on SAE form.	Section 8.1 AE Reporting Requirements
Added updated text from April 2023 protocol template where applicable.	To align with current protocol template language version April 2023 to ensure regulatory compliance.	Section 10 (QUALITY CONTROL AND QUALITY ASSURANCE); Section 11.1, 11.3 (DATA HANDLING AND RECORD KEEPING); Section 12 (ETHICS); Section 15.1, 15.2 (PUBLICATION OF STUDY RESULTS)
Added "QTL"to abbreviation table in Appendix 1. Added FVIIa to abbreviation table in Appendix 1.	To align with updated QTL text and definition from Section 10. To clarify definition of acronyms.	Appendix 1
Added "New Untreated Bleed" definition to Appendix 2 to align with language in the SAP.	Minor clarifications for consistency with the SAP.	Appendix 2
Incorporated an administrative change from the protocol administrative change letter (PACL#15) dated 22 November 2022.	To clarify the definition of a bleed that necessitates administration of coagulation factor within 72 hours of signs and symptoms of bleeding is referred to as a "treated bleed".	Appendix 2

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APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier[a]	**Screening Visit**	**Baseline Visit (on-site or remote**[i]**; start of data collection)**	**Interim Phone Call**	**End of Study/Early Termination Visit**[j]
Visit Window	Day -42 to Day -1	Day 1	Approximately every 30 days from Day 1 ±1 week	See Footnote [j]
Informed Consent[b]	X			
Medical History/Hemophilia History and Demography[c]	X			
Vitals (temperature (°C), blood pressure (sitting), pulse and respiration), body weight (kg) and height (cm)	X			
Factor IX/FVIII activity, HBV, HCV, liver fibrosis, and HIV serology (viral load and CD4 count for HIV positive participants only) Laboratory Sample Collection[d]	X			
Neutralizing Antibody (nAb) Laboratory Sample Collection for both AAV-Spark-100 and AAV6[e]	X			
nAb Laboratory Assessment[e]	X			
Eligibility Confirmation		X		
Electronic Diary Training[f]	X (Screening Visit–Baseline Visit)			
Issue Electronic Diary (nAb negative participants only)[g]		X		
Review Electronic Diary		X	X	X
Return Electronic Diary				X
Concomitant treatments	X →→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→X			

Visit Identifier[a]	Screening Visit	Baseline Visit (on-site or remote[i]; start of data collection)	Interim Phone Call	End of Study/Early Termination Visit[j]
Serious and non-serious adverse event monitoring[h]	X →→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→X			

a. The screening visit should occur within 42 days of the start of the baseline visit (Day 1). If there is no documentation of baseline Factor IX/VIII activity (≤2% or ≤1%, respectively, in participant's medical record) or no documentation of HBV, HCV, liver fibrosis, and HIV serology (viral load and CD4 count for HIV positive participants only) within the last 12 months prior to screening (6 months for HCV), then participants will need to undergo laboratory testing prior to baseline visit to determine their status. The screening period may be extended upon consultation with the sponsor's medical monitor. Reason for the extension must be recorded in the source documents. Prior to baseline visit (Day 1), the study site will notify participants of their nAb laboratory results to determine participant eligibility to continue in the study and the subsequent data collection phase. Neutralizing antibody positive participants will be discontinued from further participation in the study and nAb negative participants will schedule a baseline visit to continue in the study and the subsequent data collection phase. It is required that the interim phone call(s) will occur approximately every 30 days from baseline visit (Day 1). These phone calls will ensure participant's study compliance with their electronic diary and standard of care regimen, and monitor participant safety by recording any serious adverse events or any protocol specified non serious adverse events (see Section 8.1).

b. Informed consent should be obtained from participants prior to any study related procedures. Refer to Section 6.1 for additional details.

c. Demographics include sex/gender, race, date of birth (month and year only), and ethnicity. Hemophilia history includes (but is not limited to) date of diagnosis, severity, history of inhibitor (FIX inhibitor for hemophilia B participants or FVIII inhibitor for hemophilia A participants), family inhibitor history, gene mutation (if available), number of exposure days, number of bleeds and infusions within the last 12 months (where available), and current FIX or FVIII treatment and regimen.

d. If there is no documentation of baseline Factor IX/VIII activity (≤2% or ≤1% respectively in participant's medical record); or no documentation of HBV, HCV, liver fibrosis (FibroScan OR FibroTest/FibroSURE), and HIV serology (viral load and CD4 count for HIV positive participants only) within the last 12 months prior to screening (6 months for HCV), then participants will need to undergo laboratory testing prior to baseline visit to determine their status. In the absence of a documented FIX:C or Factor VIII (FVIII:C) activity level (according to the underlying disease) participants will observe a minimum 72 hour FIX or FVIII washout for recombinant or plasma derived products or a minimum of 5-10 days or longer for extended half-life products prior to the baseline visit. Depending on when the last FIX or FVIII dose was administered before the beginning of the FIX or FVIII washout, an interval longer than 72 hours or 5 10 days may be needed. The screening visit window may be extended, upon consultation with the sponsor's medical monitor. Reason for the extension must be recorded in the source documents. If a participant sustains a bleed requiring treatment during the ≥72 hour or ≥5-10 day FIX or FVIII washout, the necessary treatment should be administered using the participant's usual FIX or FVIII replacement product. Once the bleed has been adequately treated, the screening visit must be rescheduled, and must be preceded by a new ≥72 hour or ≥5-10 day FIX or FVIII washout.

e. Prior to baseline visit (Day 1), upon the availability of the nAb laboratory results, the study site will notify participants of their nAb laboratory test results via a telephone call. The nAb positive participants (nAb positive against AAV-Spark100 for hemophilia B population or nAb positive against AAV6 for hemophilia A population) will be contacted to explain what the implications of being nAb positive are and subsequently discontinued from further participation in the study. The nAb negative participants (nAb negative against AAV-Spark100 for hemophilia B population or nAb negative against AAV6 for hemophilia A population) will be contacted to schedule a baseline visit to issue their electronic diary and continue on with the data collection phase. In the hemophilia B population, the samples collected during the screening visit may be used to test nAb against AAV6, as well as testing for antibodies against additional AAVs, at the end of the study (Note: Hemophilia B participants screened prior to Amendment 5 will be reconsented prior to testing their

Visit Identifier[a]	Screening Visit	Baseline Visit (on-site or remote[i]; start of data collection)	Interim Phone Call	End of Study/Early Termination Visit[j]

previously collected samples for nAb against AAV6, as well as testing for antibodies against additional AAVs). The nAb result against AAV6, as well as antibodies against additional AAVs, will not be shared with the hemophilia B participants. In the hemophilia A population, the samples collected during the screening visit may be used to test nAb against AAV-Spark100, as well as testing for antibodies against additional AAVs, at the end of the study. The nAb result against AAV-Spark100, as well as antibodies against additional AAVs, will not be shared with the hemophilia A participants.

f. Training with respect to operation of the electronic diary including timing and information to be entered by the participant may be conducted at the screening or baseline visit. Refer to Sections 6.1 and 6.2 for additional details.

g. The electronic diary will capture the following: FIX/FVIII replacement therapy administration (date, time, reason for administration, and dose [IU]); and bleeding events (date, location and whether the etiology is spontaneous or traumatic). See Sections 6.2 and 6.3. The reasons for preventative FIX/FVIII replacement therapy will be captured in eCRF.

h. Adverse events will be recorded from consent through the end of study visit. Any SAE experienced by the participant from the day of signing the ICD through end of study visit is to be recorded, regardless of the severity of the event or its relationship to standard of care therapy. Protocol specified non serious adverse events (re: Section 8.1) are to be recorded from consent through end of study visit regardless of severity of the event or its relationship to standard of care therapy.

i. In the event an on-site clinic study visit cannot be conducted, the investigator and/or site staff can conduct a remote visit (if permitted by local regulations). The remote visit can be conducted with investigator site staff via telehealth (eg, audio,video,video conferencing software). Refer to Section 6 for additional details.

j. The duration of follow-up for participants in this study (C0371004) will be at least 6 months until the required number of treated participants in the respective treatment protocols (C0371002 and C3731003) are met (refer to Section 9.1 for sample size determination). Subsequent to reaching the required number of participants in the treatment protocols, the exact duration of follow-up for each individual participant may vary. The end of study visit marks the conclusion of the data collection phase and completion of the study for each participant. Participants withdrawing from the study prematurely will complete a termination visit and must have end of study assessments performed unless they have withdrawn consent.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

The C0371004 study does not involve use of an investigational product. The study is designed to evaluate current Factor IX (FIX) or Factor VIII (FVIII) prophylaxis replacement therapy, in the usual care setting of moderately severe to severe adult hemophilia B participants (FIX:C≤2%) who are negative for neutralizing antibodies (nAb) to adeno-associated virus vector (AAV)-Spark100 OR moderately severe to severe adult hemophilia A participants (Factor VIII circulating [FVIII:C] ≤1%) who are negative for nAb to AAV6 (capsid portion of SB-525).

1.2. Background and Rationale

Hemophilia B (Christmas disease) and hemophilia A are hereditary X-chromosomal recessive bleeding disorders caused by deficiency or absence of coagulation factors: FIX (encoded by F9) in hemophilia B and FVIII (encoded by F8) in hemophilia A.[2] Hemophilia has an estimated frequency of ~1/10,000 births; hemophilia A is more common than hemophilia B, representing 80–85% of the total hemophilia population.[3]

Severity of hemophilia is operationally defined into 3 categories based on circulating FIX or FVIII activity levels in the plasma each of which is characterized by different bleeding profiles. Patients with severe hemophilia have factor activity (FIX in hemophilia B and FVIII in hemophilia A) levels less than 1% (or <1 IU/dL) of normal while patients with moderate hemophilia have factor activity levels 1-5% (1-5 IU/dL) of normal, and mild hemophilia patients have factor activity levels over >5-<40% (>5-<40 IU/dL) of normal.[1]

Hemophilia is characterized by bleeding into muscle, soft tissue, and joints (hemarthroses) that occur spontaneously or in response to trauma. Other types of bleeding events that may be observed include intracranial hemorrhage, bleeding following tooth extraction, post-surgical bleeding, hematomas and mucosal bleeding.[4]

Patients with hemophilia B or A are usually managed by replacing the missing or defective factor (FIX in hemophilia B and FVIII in hemophilia A) for treatment or prevention of hemorrhage. Current treatment paradigms for both hemophilia B and A rely on replacement of the missing clotting Factor IX/VIII using plasma-derived or recombinant factor administered in the setting of an acute bleed (on-demand) or at regularly scheduled intervals (prophylaxis). Venous access via peripheral veins remains the only option for the administration of Factor IX or VIII replacement therapy.[1,2,3]

Unmet medical needs associated with current methods of treatment for hemophilia include the challenging dose schedule (from 1-4 times per week to twice per month according to treatment used- standard half-life/extended half-life), burden to patients and obstacles to implementation of prophylaxis associated with replacement factor treatment (standard half-life recombinant or plasma derived clotting factor concentrates, long acting clotting factor) or new treatment with different mechanism of action (ie, antibodies like emicizumab).[5]

Gene therapy is a new treatment modality for patients with hemophilia that works via gene transfer to target cells (hepatocytes in the case of hemophilia) where Factor IX or Factor VIII is then expressed, processed and excreted into the circulation. This therapy would potentially allow patients to realize the benefit of Factor IX or Factor VIII replacement without the need for frequent intravenous infusions.

The major benefit of gene therapy is that it may provide persistent treatment of hemophilia by continuous endogenous production of functional FIX or FVIII thereby providing relief from the medical and life-style burden of recurrent on-demand or routine prophylactic protein replacement therapy.

Adeno-associated virus (AAV) based vectors have emerged as the vehicle of choice to deliver the Factors IX and VIII genes for gene therapy-based treatment of hemophilia B or hemophilia A, respectively. However, prior infection with naturally occurring AAV induces a humoral response which will render AAV-mediated transgene delivery ineffective by preventing hepatocyte transduction.

Gene therapy in hemophilia B:

Fidanacogene elaparvovec (PF-06838435; formerly SPK-9001) is an AAV-based vector designed by Spark Therapeutics for the treatment of hemophilia B. It is composed of AAV-Spark100 (a bio-engineered AAV capsid derived from a naturally occurring AAV serotype) encoding hFIX-Padua that has been shown in vitro and in a small sample of patients to be less prone to neutralization than other AAV serotype gene therapy-based vectors. However, these data are of limited scope and the geographic distribution impact on neutralizing antibodies is not currently known.

Gene therapy in hemophilia A:

Giroctocogene fitelparvovec (PF-07055480; formerly SB-525) is an AAV-based vector designed by Sangamo Therapeutics for the treatment of hemophilia A. It is composed of recombinant adeno-associated virus 2/6 (rAAV2/6) vector encoding the cDNA for the B-domain deleted (BDD) human FVIII (hFVIII) that has been shown in vitro and in a small sample of patients to be less prone to neutralization than other AAV serotype gene therapy-based vectors. However, these data are of limited scope and the geographic distribution impact on neutralizing antibodies is not currently known.

The aim of this study is to assess prospective efficacy of FIX or FVIII prophylaxis replacement therapy in the usual care setting of moderately severe to severe hemophilia B or hemophilia A participants, respectively, whose nAb to AAV-Spark100 (hemophilia B participants) and nAb to AAV6 (hemophilia A participants) are below the established thresholds (negative). The FIX and FVIII prophylaxis efficacy data obtained in this study will serve as the control for comparison with post gene therapy efficacy for those participants that subsequently enroll into and are treated in the respective subsequent Phase 3 gene therapy dosing studies (C0371002 hemophilia B and C3731003 hemophilia A).

There is no single reference safety document (SRSD) for this protocol with each product supported by their respective approved product label.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Efficacy Endpoint(s):

• To establish prospective efficacy data of:
  • FIX prophylaxis replacement therapy in the usual care setting of hemophilia B participants, who are negative for nAb to AAV-Spark100.
  • FVIII prophylaxis replacement therapy in the usual care setting of hemophilia A participants, who are negative for nAb to AAV6.
	Primary Endpoint
	• Annualized bleeding rate (ABR) in hemophilia B participants.
	• Annualized bleeding rate (ABR) in hemophilia A participants.
	Secondary Endpoint
	• Annualized number of infusions (AIR) in hemophilia B participants.
	• Annualized number of infusions (AIR) in hemophilia A participants.
	Other Secondary Endpoints
	• Dose and total factor consumption in hemophilia B participants.
	• Dose and total factor consumption in hemophilia A participants.
	• Number of bleeding events (spontaneous and/or traumatic) in hemophilia B participants.
	• Number of bleeding events (spontaneous and/or traumatic) in hemophilia A participants.

Secondary Objective(s):	**Safety Endpoint(s):**

• Evaluate safety (serious adverse events and medically important events of FIX or FVIII inhibitor, thrombotic and factor hypersensitivity reactions) of FIX replacement therapy in hemophilia B participants or FVIII replacement therapy in hemophilia A participants.	• Incidence of serious adverse events in hemophilia B participants.
	• Incidence of serious adverse events in hemophilia A participants.
	• Events of Special Interest in hemophilia B participants:
	  • FIX inhibitor;
	  • Thrombotic events;
	  • Factor hypersensitivity events.
	• Events of Special Interest in hemophilia A participants:
	  • FVIII inhibitor;
	  • Thrombotic events;

	• Factor hypersensitivity events.
Exploratory Objective(s):	**Exploratory Endpoint(s):**
• Measure the frequency of nAb against AAV-Spark100 and AAV6 in the respective populations assessed (hemophilia B or hemophilia A participants).	• The frequency and percentage of nAb status to AAV-Spark100 or AAV6 (positive, negative).

3. STUDY DESIGN

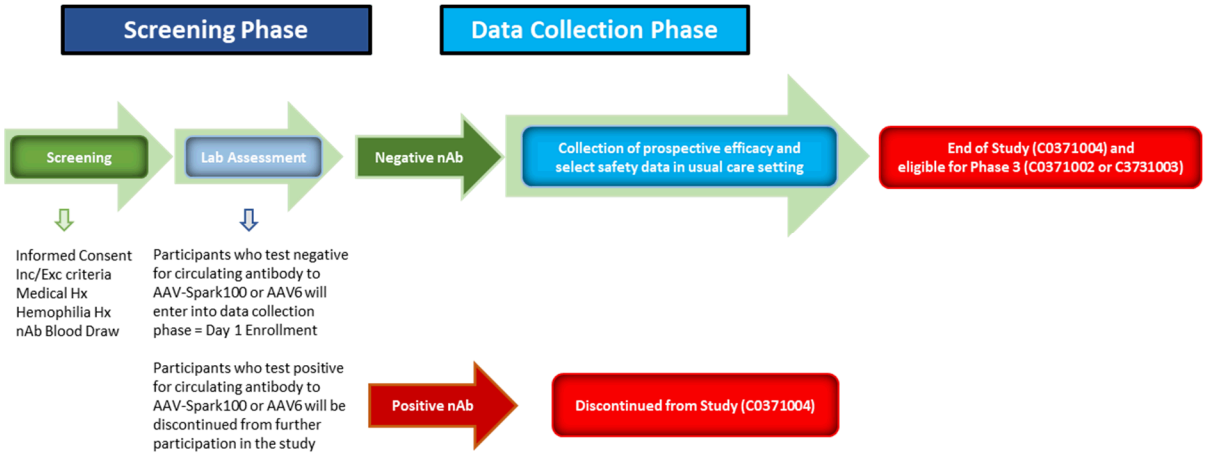
The C0371004 study will be conducted as an open-label, non-investigational product, prospective, multi-center, lead-in study to assess efficacy and selected safety data of current Factor IX (FIX) or Factor VIII (FVIII) prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia B participants (FIX:C≤2%) who are negative for nAb to AAV-Spark100 or moderately severe to severe adult hemophilia A participants (FVIII:C≤1%) who are negative for nAb to AAV6, prior to the respective therapeutic Phase 3 gene therapy studies.

The study consists of two phases: the screening phase will include a laboratory blood draw to determine nAb status to both AAV-Spark100 or AAV6 for each respective group of participants (hemophilia B or hemophilia A) and the second phase will be the data collection phase for those hemophilia B participants who are below the established threshold for nAb to AAV-Spark100 or those hemophilia A participants who are below the established threshold for nAb to AAV6. The data collection phase is designed to provide prospective efficacy and selected safety data of FIX prophylaxis replacement therapy in the usual setting of those hemophilia B participants or FVIII prophylaxis replacement therapy in the usual setting of those hemophilia A participants.

Sample size in this study is driven by the need to meet a required number of treated participants in the respective treatment protocols (C0371002 and C3731003). The duration of follow-up for participants in this study (C0371004) will be at least 6 months until the required number of treated participants in the respective treatment protocols (C0371002 and C3731003) are met (refer to Section 9.1 for sample size determination). Subsequent to reaching the required number of participants in the treatment protocols, the duration of follow-up for participants recruited into this study (C0371004) may vary.

Participants withdrawn from this study or the subsequent treatment study may be replaced, at the discretion of the investigator and sponsor. The total duration of the study including enrollment period will be approximately 60 months.

Figure 1. Study Schematic



4. PARTICIPANT ELIGIBILITY CRITERIA

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

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before participants are included in the study.

4.1. Inclusion Criteria

Participants in each population (Hemophilia B or A) must meet **all** of the inclusion criteria for that population to be eligible for enrollment into the study:

Hemophilia B Population:

1. Evidence of a signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, FIX prophylaxis treatment plan, laboratory tests and other study procedures.

3. Males ≥18 and <65 years of age with moderately severe to severe hemophilia B and documented FIX activity (≤2%) prior to baseline visit.

4. Previous experience with FIX therapy (≥50 documented exposure days to a FIX protein product such as recombinant, plasma-derived or extended half-life FIX product).

5. Participants on FIX prophylaxis replacement therapy (recombinant, plasma-derived or extended half-life FIX product) must have the intention to remain on FIX prophylaxis replacement therapy for the duration of the study.

6. No known hypersensitivity to FIX replacement product.

7. No history of FIX inhibitor (clinical or laboratory-based assessment) defined as a titer ≥0.6 BU/mL, regardless of the laboratory normal range, or any measured Bethesda inhibitor titer greater than the upper limit of normal for the laboratory performing the assay. Clinically, no signs or symptoms of decreased response to FIX administration. Participants will not be required to undergo diagnostic evaluation of inhibitor status to participate in the study.

Hemophilia A Population:

1. Evidence of a signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

2. Willing and able to comply with scheduled visits, FVIII prophylaxis treatment plan, laboratory tests and other study procedures.

3. Males ≥18 and <65 years of age with moderately severe to severe hemophilia A and documented FVIII activity (≤1%) prior to baseline visit.

4. Previous experience with FVIII therapy (≥150 documented exposure days to a FVIII protein product such as recombinant, plasma-derived or extended half-life FVIII product).

5. Participants must be on a stable FVIII prophylaxis replacement therapy (recombinant, plasma-derived or extended half-life FVIII product) at study entry and must have the intention to remain on FVIII prophylaxis replacement therapy for the duration of the study. This does not include nonfactor treatments (eg. Emicizumab), which are prohibited, see Section 5.4.

6. No known hypersensitivity to FVIII replacement product.

7. No history of FVIII inhibitor (clinical or laboratory-based assessment) defined as a titer ≥0.6 BU/mL, regardless of the laboratory normal range, or any measured Bethesda inhibitor titer greater than the upper limit of normal for the laboratory performing the assay. Clinically, no signs or symptoms of decreased response to FVIII administration. Participants will not be required to undergo diagnostic evaluation of inhibitor status to participate in the study.

4.2. Exclusion Criteria

Participants with any of the following characteristics/conditions will not be included in the study:

1. Anti-AAV-Spark100 neutralizing antibody titer above the established threshold performed by a central laboratory during screening in hemophilia B participants or Anti-AAV6 neutralizing antibody titer above the established threshold performed by a central laboratory during screening in hemophilia A participants.

2. Lack of participant compliance with documentation of bleeds and/or prophylaxis replacement therapy administration.

3. If there is no documentation regarding hepatitis status, as defined below, within the last 12 months prior to screening for hepatitis B and 6 months prior to screening for hepatitis C, then participants will be required to have the following hepatitis testing performed at screening:

a. Hepatitis B screening (acute and chronic):

HBsAg (also referred to as Hepatitis B surface antigen),
HBV-DNA viral assay (also referred to as a nucleic acid test for Hepatitis B virus DNA), and Anti-HBc (also referred to as Total Hepatitis B core antibody).

- A participant is not eligible if either HbsAg is positive or HBV-DNA is positive/detectable.

- Anti-HBc must be obtained in all participants for determination of whether the participant had prior hepatitis B. If the anti-HBc is positive and both HBsAg and HBV DNA are negative this would be consistent with a *prior* infection and the participant would be eligible for the study. Anti-HBc must be obtained in all participants to discriminate between those with no prior hepatitis B and those with prior infection in the event of reactivation. FDA has noted reactivation of hepatitis B virus exists.

- One documented negative HBV-DNA viral load is sufficient to assess eligibility. A participant who is currently undergoing anti-viral therapy for hepatitis B is not eligible.

b. Hepatitis C (acute or chronic):

- A participant who is currently undergoing anti-viral therapy for chronic hepatitis C is not eligible.

- Participants treated with anti-viral therapy for chronic hepatitis C, must have completed anti-viral therapy at least 6 months prior to screening and have a negative HCV-RNA at least 6 months prior to screening.

- All participants (who are not currently undergoing anti-viral therapy for chronic hepatitis C) must have a single HCV-RNA load assay (also referred to as a nucleic acid test [NAT] for HCV RNA**)** obtained during the 6 months preceding screening. This includes participants with prior known chronic hepatitis C who have completed treatment with anti-viral therapy.

- A participant is not eligible if his HCV-RNA load assay result is positive/detectable.

4. Currently on antiviral therapy for hepatitis B or C.

5. Significant liver disease, as defined by pre-existing diagnosis of portal hypertension, splenomegaly, or hepatic encephalopathy.

   All participants who do not have the listed pre-existing diagnoses above *must* have the following assessments performed within the last 12 months prior to screening and if not will need to be tested for liver fibrosis status at screening: a serum albumin level below normal limits and/or significant liver fibrosis by any of the following diagnostic modalities: FibroScan median stiffness score >8 kPa units OR FibroTest/FibroSURE >0.48*.

   * NOTE: If there is concern regarding the validity of any of the liver fibrosis test results please contact the medical monitor to discuss whether any additional testing needs to be performed (ie, either repeating any test or performing another fibrosis test). Also, note, if a participant has a known history of Gilbert's syndrome, a FibroTest cannot be used for fibrosis testing.

6. Documented serological evidence of human immunodeficiency virus HIV-1 or HIV-2 with Cluster of Differentiation 4 positive (CD4+) cell count ≤200 mm^3 within the last 12 months prior to screening. Participants who are HIV positive and stable, have an adequate CD4 count (>200/mm^3) and undetectable viral load (<50 gc/mL) documented within the preceding 12 months, and are on an antiretroviral drug regimen are eligible to enroll. Participants who have not been tested within the prior 12 months of screening will need to be tested for HIV status at screening.

7. History of chronic infection or other chronic disease that the investigator deems an unacceptable risk. In addition, any participant with conditions associated with increased thromboembolic risk such as known inherited or acquired thrombophilia, or a history of thrombotic events including but not limited to stroke, myocardial infarction, and/or venous thromboembolism, is excluded.

8. Any concurrent clinically significant major disease or condition that the investigator deems unsuitable for participation or other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study. In addition, any participant with a history of a neoplasm (including hepatic malignancy) that required treatment (eg, chemotherapy, radiotherapy, immunotherapy), is excluded, except for adequately treated basal or squamous cell carcinoma of the skin or a surgically removed benign neoplasm not requiring chemotherapy, radiotherapy and/or immunotherapy. Any other neoplasm that has been cured by resection should be discussed between the investigator and sponsor.

9. Participation in other studies if involving administration of investigational product(s) within the last 3 months prior to study entry and/or during study

participation or in a previous gene therapy clinical study within the last 12 months prior to screening.

- Participants already enrolled in this lead-in study (C0371004) may be allowed to participate in the screening and baseline periods of either C0371002 or C3731003 protocols prior to their completion of the end of study visit in this lead-in study.

10. Any participant who previously received fidanacogene elaparvovec (hemophilia B) or giroctocogene fitelparvovec (hemophilia A) or any AAV gene-based therapy.

11. Participants using restricted therapies. See Section 5.4 for therapies not allowed during study participation.

12. Any participant with a planned surgical procedure requiring FIX (hemophilia B) or FVIII (hemophilia A) surgical prophylactic factor treatment in the next 24 months.

13. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or participants who are Pfizer employees, including their family members, directly involved in the conduct of the study.

NOTE: The sponsor's medical team should be contacted if there are any questions regarding any of the inclusion or exclusion criteria (Sections: 4.1 and 4.2).

4.3. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/team SharePoint site/study portal.

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

4.4. Screen Failures

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

Study participants who do not meet the criteria for participation in this study (for example, screening laboratory results and/or FibroScan results) and are deemed a screen failure, may be rescreened, because these laboratory and/or Fibroscan results can change over time. The repeated central laboratory and/or Fibroscan results must be available prior to the Baseline Visit and be within range for the participant to be eligible. Rescreened participants are required to sign a new ICD and will be assigned a different participant number.

Note: Study participants who are not deemed a screen failure, and have a test value (eg, central laboratory and/or Fibroscan) that is outside the range specified by the exclusion criteria, repeated by the central laboratory to determine eligibility. However, the new result must be available prior to the Baseline Visit and be within range for the participant to be eligible.

5. STUDY TREATMENTS

No investigational product will be administered in this study. Hemophilia B or Hemophilia A participants will remain on their current FIX or FVIII replacement therapy, respectively, using their usual prophylaxis regimen. Investigators can consult the appropriate prescribing information for the prophylaxis therapy.

5.1. Allocation to Treatment

The investigator's knowledge of the participant's current FIX or FVIII prophylaxis replacement therapy regimen should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. The study will be conducted as an open-label and non-randomized trial.

The investigator will assign all participant identification numbers sequentially to their participants as they are screened for the study. This identifying number will be retained throughout the study and remains confidential. A participant number must never be reassigned or reused for any reason. The investigator must maintain a confidential study log linking the participant number to the participant's name.

5.2. Participant Compliance

It is recommended that the study site will review participant compliance on a weekly basis but at a minimum monthly to align with the interim phone call to confirm participant compliance with electronic diary entry. The investigator, along with the sponsor will determine if a participant should be withdrawn from the study due to a participant's non-compliance which could be damaging to the study results or the participant's best

interests. Participants who are withdrawn for non-compliance or any other reason will have an Early Termination Visit.

5.3. FIX or FVIII Replacement Therapy Supplies

5.3.1. Dosage Form(s) and Packaging

No investigational product will be supplied by the sponsor. According to the underlying disease, participants will continue to administer their respective FIX or FVIII replacement therapy using a prophylaxis regimen. The frequency and dosage for their replacement therapy will be based on the approved product label for their respective therapy and adjusted solely according to medical and therapeutic necessity at the discretion of the investigator. All treatment decisions will follow the general clinical practice/standard of care and will not be influenced by the participant taking part in this study.

5.3.2. FIX or FVIII Replacement Therapy Storage

The respective FIX or FVIII replacement therapy utilized during the course of this study should follow the storage conditions stated on the product label.

5.4. Concomitant Treatment(s)

Allowed Therapy

During the study, participants are to continue with their respective FIX or FVIII prophylaxis therapy which is part of their usual treatment regimen. In addition, certain non-steroidal anti-inflammatory drugs (NSAIDs) are permitted (eg, COX-2 inhibitors and topical NSAIDs), along with HIV therapy, where medically necessary and according to standard of care.

Once a participant has signed the informed consent, they should be instructed to contact the study site to discuss any new medications, including non-prescription drugs and herbal preparations, with the investigator prior to taking them for the duration of the study.

Other therapies considered necessary for the participant's welfare may be given at the discretion of the investigator. All such therapies must be documented in the participant's medical notes and recorded in the electronic case report form (eCRF).

Disallowed Therapy

The following concomitant medications are not permitted during the study:

- Blood products such as red blood cells (RBC), platelets, and fresh frozen plasma, except for example during a surgery or another medical condition at discretion of the principal investigator (eg, after severe haemorrhage, hypovolemic shock, etc.).
- Medications known to inhibit platelet function (eg, acetylsalicylic acid (aspirin), ibuprofen, or naproxen); however, certain NSAIDs are permitted (eg, COX-2 inhibitors and topical NSAIDs). Please contact the sponsor's medical monitor if there are any questions regarding the use of medications that may prolong bleeding.

- Concomitant use of another investigational product(s).

- Bypassing agents (eg, factor VIIa, activated prothrombin complex concentrate) and nonfactor treatment (eg, emicizumab), except in situations where it is medically necessitated.

- Antifibrinolytics (e.g. tranexamic acid, aminocaproic acid), except where medically indicated.

6. STUDY PROCEDURES

Remote Baseline Visit: If permitted by local regulations, the baseline visit may be conducted as a remote visit, where participants do not go to a site to complete the baseline visit but the baseline visit can be conducted by the investigator and/or site staff via telehealth (eg, audio, video, video conferencing software). The end of study visit will be conducted on site.

6.1. Screening Visit – Screening Phase to Determine nAb Status and Eligibility into Data Collection Phase (Day -42 to Day -1)

All screening procedures must be completed within 42 days of Day -1. No study-related procedures may be performed until the Informed Consent process is completed. The following procedures will be performed prior to participant enrollment:

- Obtain written informed consent. Collect and record participant demography (including date of birth (month and year), sex/gender, race, and ethnicity).

- Collect medical history.

- Collect hemophilia history including (but is not limited to) date of diagnosis, severity, history of inhibitor (FIX inhibitor for hemophilia B participants or FVIII inhibitor for hemophilia A participants), family inhibitor history, gene mutation (if available), number of exposure days, number of bleeds and infusions within the last 12 months (where available), and current FIX or FVIII treatment and regimen.

- Collect vital signs (temperature [°C], blood pressure [sitting], pulse and respiration), body weight (kg) and height (cm).

- Collect blood sample for both nAb against AAV-Spark100 (hemophilia B) and AAV6 (hemophilia A) nAb assessment (central laboratory). In the hemophilia B population, the samples collected during the screening visit may be used to test nAb against AAV6, as well as testing for antibodies against additional AAVs, at the end of the study (Note: Hemophilia B participants screened prior to Amendment 5 will be reconsented prior to testing their previously collected samples for nAb against AAV6, as well as testing for antibodies against additional AAVs). The nAb result against AAV6, as well as antibodies against additional AAVs, will not be shared with the hemophilia B participants. In the hemophilia A population, the samples collected during the screening visit may be used to test nAb against AAV-Spark100, as well as

testing for antibodies against additional AAVs, at the end of the study. The nAb result against AAV-Spark100, as well as antibodies against additional AAVs, will not be shared with the hemophilia A participants.

  - Approximately 20 mL (4 teaspoons) of blood.

- Samples will be collected for the following tests (central laboratory): Factor IX/VIII activity (if there is no documentation), HBV, HCV, liver fibrosis (FibroScan OR FibroTest/FibroSURE), and HIV serology (viral load and CD4 count for HIV positive participants only), only if there is no documentation within the last 12 months prior to screening (6 months for HCV):

  - Approximately 20 mL (4 teaspoons) of blood.

- Review inclusion and exclusion criteria.

- Record adverse events (reference Section 8.1 for protocol specified adverse event reporting) in addition to any research-related injury adverse event arising through screening blood draw collection.

- Record concomitant treatments (drug and non-drug).

In the absence of a documented FIX:C or FVIII:C level (according to the underlying disease) participants will observe a minimum 72-hour FIX or FVIII washout for recombinant or plasma derived products or a minimum of 5-10 days or longer for extended half-life products prior to the baseline visit. Depending on when the last FIX or FVIII dose was administered before the beginning of the FIX or FVIII washout, an interval longer than 72 hours or 5-10 days may be needed. The screening visit window may be extended, upon consultation with the sponsor's medical monitor. Reason for the extension must be recorded in the source documents. If a participant sustains a bleed requiring treatment during the >72-hour or >5-10 day FIX or FVIII washout, the necessary treatment should be administered using the participant's usual FIX or FVIII replacement product. Once the bleed has been adequately treated, the screening visit must be rescheduled, and must be preceded by a new >72-hour or >5-10 day FIX or FVIII washout prior to baseline visit (Day 1), upon the availability of the nAb laboratory test results, the study site will notify participants of their nAb laboratory test results via a telephone call.

Hemophilia B Population**s**: Neutralizing antibodies against AAV-Spark100 transgene product positive participants will be contacted to explain what the implications of being nAb positive are and subsequently discontinued from further participation in the study. Neutralizing antibodies against AAV-Spark100 negative participants will be contacted to schedule a baseline visit to issue their electronic diary and continue on with the data collection phase.

Hemophilia A Population: Neutralizing antibodies against AAV6 positive participants will be contacted to explain what the implications of being nAb positive are and subsequently discontinued from further participation in the study. Neutralizing antibodies against AAV6

negative participants will be contacted to schedule a baseline visit to issue their electronic diary and continue on with the data collection phase.

For both the hemophilia B and hemophilia A populations, site staff should conduct electronic diary training with the study participant at the screening visit if the baseline visit will be conducted remotely.

- For Diary and Device Training at Screening Visit:
    - Site to provide Contact Authorization Form (CAF) for study participant to review and sign.
    - The site will need to log into mPal and add the study participant. Please activate the device using the Activation Code (found on the mPal study participant profile in lime green letters). Once Trial Guide is activated, the study participant can navigate to the "Diary" tab and complete the "Training Infusion Log" and the "Training Bleed Log".
    - Study Participant Eligible (nAb negative):
        - The site to ship the activated device to the study participant's home prior to the baseline visit.
    - Study Participant Ineligible (nAb positive):
        - Please log in to mPal, find and click on the study participant ID and click "Archive". Select "Screen fail" as the reason for archival. Clear all push notifications from the device and confirm that the Trial Guide mobile application has the "Activation Code" screen showing.

6.2. Baseline Visit – Enrollment into Data Collection Phase (Day 1)

Participants who test negative for circulating Immunoglobulin G (IgG) antibody to AAV-Spark100 and AAV6 and remain eligible (based on inclusion/exclusion criteria) will be given an electronic diary along with instructions on how to complete so that they can begin recording their FIX or FVIII replacement therapy efficacy data. If bleeding episodes or treatments are not entered or cannot be entered (ie, device left at home by mistake) in the electronic diary during the appropriate time window, data should be entered by the investigator (or site staff member) according to the CRF completion guidelines with required source documentation in the participant's medical record. The reasons for preventative FIX/FVIII replacement therapy will be captured in eCRF. The bleeding episodes and exogenous FIX/FVIII replacement data mentioned above will be referred to as "electronic diary data" regardless of how it is collected (ie, via the handheld device or according to the CRF completion guidelines).

The following procedures and assessments will be performed:

- Confirm eligibility.

- Record adverse events (reference Section 8.1 for protocol specified adverse event reporting) in addition to any research-related injury adverse event arising through screening blood draw collection.

- Provide electronic diary and training (if not already conducted at the screening visit with site staff) with respect to operation of the electronic diary including timing and information to be entered by the participant, specifically:

  - FIX/FVIII replacement therapy administration (date, time, reason for administration, and dose international unit [IU]).

  - Bleeding events as assessed by the participant (date, time, location and whether they are trauma related or spontaneous), should reference Appendix 2 as guidance on reporting such events.

- Record concomitant treatments (drug and non-drug).

- If necessary, FIX/FVIII inhibitor, FIX/FVIII activity can be done at investigator's discretion and per their local usual standard of care. Whenever FIX/FVIII activity is assessed, the time (Date/Hour) of previously administered last dose of FIX/FVIII replacement product or blood product should be captured in the electronic diary.

6.3. Data Collection – Collection of FIX/FVIII Replacement Therapy and/or Safety Events (Day 1 through End of Study/Early Termination For Each Participant)

Neutralizing antibody negative participants will continue with data collection until the End of Study/Early Termination Visit.

Study participants will record their FIX/FVIII replacement therapy administration (date, time, reason for administration, and dose [IU] and bleeding events (date, time, location and whether they are trauma related or spontaneous), in the electronic diary and should reference Appendix 2 as guidance on reporting such events. If bleeding episodes or treatments are not entered or cannot be entered (ie, device left at home by mistake) in the electronic diary during the appropriate time window, data should be entered by the investigator (or site staff member) according to the CRF completion guidelines with required source documentation in the participant's medical record. The reasons for preventative FIX/FVIII replacement therapy will be captured in eCRF. The bleeding episodes and exogenous FIX/FVIII replacement data mentioned above will be referred to as "electronic diary data" regardless of how it is collected (ie, via the handheld device or according to the CRF completion guidelines). It is recommended that the study site review participant compliance on a weekly basis but at a minimum monthly to align with interim phone call to confirm participant compliance with electronic diary entry. The study site should review any change in participant's FIX/FVIII replacement therapy administration, concomitant treatments and report any adverse events (reference Section 8.1 for protocol specified adverse event reporting) in addition to any research related injury adverse event arising through screening blood draw collection. The study site should enter this data in the eCRF accordingly. If necessary, FIX/FVIII inhibitor, FIX/FVIII activity can be done at the investigator's discretion and per their local usual standard of care. Whenever FIX/FVIII activity is assessed, the time (Date/Hour) of

previously administered last dose of FIX/FVIII replacement product or blood product should be captured in the electronic diary as well.

Any unplanned study visits prior to the End of Study/Early Termination Visit will be at the discretion of the investigator and may follow the local usual standard of care. Relevant study related data (FIX/FVIII replacement therapy, bleed events, and/or safety events) generated from an unplanned visit should be entered in the eCRF.

6.4. Interim Phone Call (Approximately Every 30 Days from Day 1 ±1 Week)

It is required that the study site call participants approximately every 30 days from baseline visit (Day 1). These phone calls ensure participant's study compliance with their electronic diary and standard of care regimen, and monitor participant safety by recording any serious adverse events or any protocol specified non-serious adverse events (see Section 8.1), along with any changes to their routine medical care (ie, changes to concomitant therapies) from previous interim phone call.

6.5. End of Study/Early Termination

The end of study visit marks the conclusion of the data collection phase and completion of the study for each participant. Participants withdrawing from the study prematurely will complete a termination visit and must have end of study assessments performed unless the participants have withdrawn consent.

The following procedures and assessments will be performed. Participants withdrawing from the study prematurely must also have these assessments performed unless the participants have withdrawn consent to have any further data collected.

- Record serious adverse events and any protocol specified non-serious adverse event (see Section 8.1).
- Record concomitant treatments (drug and non-drug).
- If necessary, FIX/FVIII inhibitor, FIX/FVIII activity can be measured at investigator's discretion and per their local usual standard of care. Whenever FIX/FVIII activity is assessed, the time (Date/Hour) of previously administered last dose of FIX/FVIII replacement product or blood product should be captured in the electronic diary.
- The investigator or qualified designee should review the electronic diary with the participant for any new data entered since last interim phone call:
    - FIX/FVIII replacement therapy administration (date, time, reason for administration, and dose [IU]).
    - The reasons for preventative FIX/FVIII replacement therapy will be captured in eCRF.

- Bleeding events as assessed and reported by the participant (date, time, location and whether they are trauma related or spontaneous), should reference Appendix 2 as guidance on reporting such events. Return electronic diary.

6.6. Participant Withdrawal

Withdrawal of consent:

Participants who request to discontinue study participation after collection of the scheduled blood sample (to assess nAb status) during the screening phase and/or entry into the data collection phase will provide no further information from the time of withdrawal of informed consent. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

In the event that vital status (whether the participant is alive or dead) is not known by the investigator from follow-up with the participant, or previously designated family member, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the participant to 1 registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the participant remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the participant's medical records.

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the participant to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's medical record. In any

circumstance, every effort should be made to document participant outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the participant return for a final visit, if applicable, and follow-up with the participant regarding any unresolved adverse events (AEs).

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

Participants who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

The only protocol-required test for this study is the nAb laboratory blood draw during the screening visit.

Every effort should be made to ensure tests and procedures are completed as described including any screening laboratory tests for Factor IX/VIII activity; HBV, HCV, liver fibrosis, and HIV serology (viral load and CD4 count for HIV positive participants only) if there is no documentation within the last 12 months prior to screening (6 months for HCV). However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8. ADVERSE EVENT REPORTING

NOTE: Exposure during pregnancy reporting throughout Section 8 is not applicable to the United Kingdom and Ireland. Lack of Efficacy reporting throughout Section 8 is only applicable to Canada.

8.1. Requirements

The table below summarizes the requirements for recording safety events on the eCRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs (including protocol specified Events of Special Interest subject to SAE reporting); (2) non-serious adverse events (AEs); and (3) scenarios involving exposure to a Pfizer or non-Pfizer product (hereafter referred to as “standard of care therapy” including medication error, lack of efficacy, exposure during pregnancy, and occupational exposure.

Safety Event	Recorded on the eCRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Protocol Defined Events of Special Interest: FIX/FVIII Inhibitor, thrombotic events, FIX/FVIII hypersensitivity reactions	All	All
Non-serious AE	• Events leading to participant withdrawal or discontinuation from the study • Events necessitating unscheduled visits to the clinic	None
Scenarios involving exposure to the standard of care therapy including medication error, lack of efficacy, exposure during pregnancy, and occupational exposure	Only AEs/SAEs associated with exposure during pregnancy. All medication errors (regardless of whether associated with an AE/SAE) All lack of efficacy (regardless of whether associated with an AE/SAE) Occupational exposure is not recorded.	All exposure during pregnancy (and EDP supplemental form for EDP), occupational exposure, lack of efficacy* (regardless of whether associated with an AE/SAE).

* LOE serious and non-serious events reportable on the CT SAE form to Pfizer safety.

For this protocol all participants will remain on their FIX/FVIII replacement therapy per standard of care and will not be receiving an investigational product. The study comprises a screening phase with one single blood draw to assess neutralizing antibody status of the participant followed by a data collection phase in accordance with routine clinical care. Based on the study design, the sponsor will restrict safety data collection to safety events outlined in the table above. Any observed or volunteered event, as outlined in the table above and regardless of suspected causal relationship to standard of care therapy will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator are to be reported regardless of whether the event is determined by the investigator to be related to standard of care therapy. In particular, if the SAE is fatal or life -threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information.

This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, eCRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the Case Report Form (CRF)

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

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the eCRF all directly observed AEs and all AEs spontaneously reported by the study participant and that are detailed in the table above. In addition, each study participant will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Participant Withdrawal section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the eCRF.

When a participant withdraws from the study because of an SAE, the SAE must be recorded on the eCRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure), through the duration of the study until their final study or early termination visit.

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

8.1.4.2. Recording Non-serious AEs and SAEs on the eCRF

During the active collection period, both non-serious AEs and SAEs are recorded on the eCRF as stated in the table above.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the eCRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that standard of care therapy caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator's final determination of causality is "unknown" and s/he does not identify whether standard of care therapy caused the event, then the event must still be reported within 24 hours. If the investigator's causality assessment is "unknown but not related" to standard of care therapy, this should be clearly documented on study records and for all AEs reported to Safety as per table above on the CT SAE Report Form.

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

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study participant administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. In this study, all participants will remain on their usual respective FIX or FVIII replacement therapy and will not be receiving an investigational product. The study comprises a screening phase with blood draw to assess nAb status of the participant followed by a data collection phase in accordance with routine clinical care. Based on the study design, the sponsor will restrict safety data collection to the following AEs:

- Any research related injury arising through blood draw collection as part of screening procedures;
- FIX/FVIII inhibitor;
- Thrombotic event;
- FIX/FVIII Hypersensitivity reaction;
- Any event leading to participant withdrawal or discontinuation from the study;
- Any event necessitating an unscheduled visit to the study site.

Hemophilia events that are likely to occur due to the participant's hemophilia (for example, bleeding and pain, swelling or decreased range of motion as a consequence of the bleed) are not reportable as AEs unless the event meets one of the criteria for AE reporting detailed in the protocol or meets SAE criteria and therein should be reported as a SAE. Consideration on whether an event is a hemophilia event is based on investigator discretion and bleeding events recorded by the participant in their electronic diary will be reviewed by the investigator and assessed against reporting obligations for S/AE.

8.2.2. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event. The protocol specified events of special interest: FIX/FVIII inhibitor, thrombotic event and FIX/FVIII hypersensitivity reaction are to be reported as SAEs.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

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

8.2.3. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);

- Social admission (eg, participant has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual participant.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with participant's usual function.
MODERATE	Interferes to some extent with participant's usual function.
SEVERE	Interferes significantly with participant's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the participant's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol Specified Serious Adverse Events

There are no protocol-specified SAEs exempt from reporting in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections and will be handled as SAEs in the safety database.

8.4.2. Exposure to Standard of Care Therapy during Pregnancy and Occupational Exposure

Exposure to the standard of care therapy during pregnancy and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.2.1. Exposure During Pregnancy

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

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a

liveborn baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the standard of care therapy.
- Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case by case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.2.2. Occupational Exposure

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

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

8.4.3. Medication Errors and Lack of Efficacy

Other exposures to the standard of care therapy may occur in clinical trial settings, such as medication errors and lack of efficacy.

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

* LOE serious and non-serious events reportable on the CT SAE form to Pfizer safety.

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of the standard of care therapy by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving participant exposure to the standard of care therapy;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

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

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

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

8.4.3.2. Lack of Efficacy

Reports of lack of efficacy to any of the respective usual FIX or FVIII replacement products are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

All data analyses will be performed separately for each population (hemophilia A and hemophilia B). There will be no joint analysis done that includes both populations together outside of the exploratory endpoint of neutralizing antibody positivity rates.

9.1. Sample Size Determination

Hemophilia B:

The sample size for this hemophilia B cohort is based on the number of evaluable participants needed for the subsequent Phase 3 registration study C0371002 (ie, N=80 to be enrolled and treated in C0371002; it is anticipated that 60 participants will have at least

6 months of follow-up data from this study [C0371004]; for the remaining participants, the duration of follow-up data from this study [C0371004] may vary depending on the timing of their enrollment into the subsequent treatment protocol [C0371002]). It is expected that the attrition rate between this study and C0371002 will be approximately 20%. Additionally, it is anticipated that approximately 10% of participants in C0371004 will not complete the study. Therefore, it is estimated that 111 participants will need to be enrolled to allow approximately 100 participants to complete study C0371004 and be eligible for enrollment into C0371002.

Hemophilia A:

The minimum sample size for this hemophilia A cohort is based on the minimum number of evaluable participants needed for the primary analysis of the subsequent Phase 3 registration study C3731003 (ie, at least N=50 with at least 6 months of follow-up data from this study [C0371004] to reach the primary analysis time point in C3731003). It was initially anticipated that approximately 20% of participants in C0371004 would not enter the C3731003 study. However, the attrition rate was higher than expected following the temporary pause in the subsequent Phase 3 study (C3731003). Therefore, it is now estimated that approximately 95 participants will need to be enrolled in this cohort to allow approximately 70 participants to be enrolled into C3731003 to provide the minimum sample size required for C3731003. A sufficient number of participants will be screened in this study [C0371004] in order to enroll approximately 95 participants.

9.2. Efficacy Analysis

All participants that signed the ICD, were subsequently identified as nAb negative (negative for circulating IgG antibody to AAV-Spark100, or negative for circulating IgG antibody to AAV6) and who participated in the prospective data collection phase as part of their usual healthcare setting will be included in the efficacy analysis set. The cohort of hemophilia B and hemophilia A participants will be analyzed separately.

9.2.1. Analysis of the Primary Endpoint

The annualized bleeding rate (ABR) per participant will be calculated as the number of bleeds over number of days from baseline visit (Day 1) to end of study x 365.25 days. ABR will be summarized using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum).

9.2.2. Analysis of Secondary Endpoints

The annualized infusion rate (AIR) per participant will be calculated as the number of infusions received over number of days from baseline visit (Day 1) to end of study x 365.25 days. AIR will be summarized using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum).

The total respective Factor IX or VIII replacement therapy consumption and the corresponding dose will be descriptively summarized by the categories of the replacement therapy, where appropriate. Infusion diary (electronic diary) of the respective Factor IX or VIII replacement therapy will be listed.

The number of bleeding episodes will be summed up by spontaneous, traumatic and overall, as defined in Appendix 2.

9.3. Analysis of Other Endpoints (Exploratory Endpoint)

9.3.1. nAb Assessment

The individual circulating IgG antibody titer, AAV-Spark100 and AAV6. nAb status will be listed for each participant in the screening phase. The frequency and percentage by nAb status (positive, negative) will be summed for all countries combined and/or regions. The cohort of hemophilia B and hemophilia A participants will be analyzed separately, as well as combined.

9.4. Safety Analysis

Safety data will be listed and summarized descriptively for each respective participant population (hemophilia B and hemophilia A) separately. The primary safety analysis will be performed on all participants that sign the informed consent document and are subsequently identified as nAb negative and are enrolled (complete baseline visit) into the study. The events of special interest (ESI) include, but not limited to, inhibitor against FIX/FVIII, thrombotic events, and FIX/FVIII hypersensitivity reactions. Frequency and percentage of these ESI events will be summarized. In addition, any events leading to discontinuation from the study will be described.

Safety data collected from those participants that sign the informed consent document and subsequently are discontinued from further participation in the study will be listed and presented separately.

9.5. Interim Analysis

There is currently no plan for a formal interim analysis.

Prior to the final analysis, there may be periodic reviews of data to support publications, regulatory submission, and responses. Periodic reviews will be conducted to provide an assessment of AAV-Spark100 and AAV6 immune status for publication (eg, abstract, manuscript). The review will be planned once the target number of participants have been enrolled into the data collection phase, if data permit. These reviews and summaries will include but may not be limited to the frequency of the positive and negative participants to the neutralizing antibody against AAV-Spark100 and AAV6, distribution of the population, range of neutralizing antibody titers, and other screening data related to hemophilia, such as hemophilia history.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The

investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the institutional review board/ethics committee (IRB/EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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

Quality Tolerance Limits (QTLs) are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician participant chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment (FIX or FVIII therapy) disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the International Council of Harmonization (ICH) guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

11.3. Data Protection

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

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

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical

code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

12. ETHICS

12.1. Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

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

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

12.2. Participant Information and Consent

All parties will ensure protection of participant personal data and will not include participant names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, participant names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study participants. The investigator site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with applicable privacy laws.

The informed consent document and any participant recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

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

The informed consent document used during the informed consent process and any participant recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each participant before any study-specific activity is performed. The investigator will retain the original of each participant's signed consent document.

12.3. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new

information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of participants have been recruited and completed the study (last participant last visit [LPLV]) as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as LPLV.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of fidanacogene elaparvovec and giroctocogene fitelparvovec at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants and the hospital pharmacy (if applicable). As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

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

Documents within marketing applications

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

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

15.2. Publications by Investigators

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

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

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

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

16. REFERENCES

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AAV	adeno-associated virus
AAV2/6	adeno-associated virus 2/6
AAV6	adeno-associated virus vector 6
AAV-Spark100	Bioengineered AAV capsid, derived from a naturally occurring AAV serotype
AAV-Spark100-hFIX19-Padua	Adeno-associated viral vector comprised of the Spark100 AAV capsid encoding hFIX-Padua
ABR	Annualized Bleeding Rate
AIR	Annualized Infusion Rate
AE	adverse event
AST	Aspartate Transaminase
BDD	B-domain deleted
BU	Bethesda Unit
CAF	Contact Authorization Form
CD4+	Cluster of Differentiation 4 positive
cDNA	Complementary DNA
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRF	case report form
CSA	clinical study agreement
CSR	clinical study report
CT	clinical trial
CTA	clinical trial application
EC	ethics committee
EDP	exposure during pregnancy
eCRF	Electronic case report form
ESI	Events of Special Interest
EU	European Union
EudraCT	European Clinical Trials Database
FIX	Factor IX
FIX:C	Factor IX Circulating
FVIIa	Factor VIIa
FVIII	Factor VIII
FVIII:C	Factor VIII Circulating
GCP	Good Clinical Practice
HBc	Hepatitis B Core
HBsAg	Hepatitis B Surface Antigen
HBV-DNA	Hepatitis B Virus – Deoxyribonucleic Acid
HCV	Hepatitis C Virus

Abbreviation	Term
HCV-RNA	Hepatitis C Virus –Ribonucleic Acid
hFVIII	human FVIII
HIV	human immunodeficiency virus
IA	interim analysis
ICD	Informed Consent Document
ICH	International Council of Harmonization
ID	identification
IgG	Immunoglobulin G
IND	investigational new drug application
IRB	institutional review board
IU	international unit
LOE	Lack of Efficacy
LPLV	last participant last visit
MAH	marketing authorization holder
MoH	Ministry of Health
N	number
N/A	not applicable
nAb	neutralizing antibody
PACL	protocol administrative change letter
PCD	primary completion date
PI	principal investigator
QTL	quality tolerance limit
rAAV2/6	Recombinant adeno-associated virus 2/6
RBC	Red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SB-525 (rAAV6-hFVIII-BDD)	Adeno-associated viral vector comprised of AAV6 capsid encoding hFVIII-BDD
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reactions
US	United States

Appendix 2. Bleed and Factor Replacement Regimen Definitions[1,2,3]

Definition of a Bleed (for analysis purposes)

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

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

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

New Untreated Bleed: An untreated bleed occurring >72 hours after the previous untreated bleed at the same site or occurring >72 hours after stopping treatment from the original bleed for which treatment was initiated, or an untreated bleed occurring at a different site from the original bleed regardless of the time from last bleed or last injection.

Definition of a Bleed Location

Target Joint: Defined as a major joint (eg, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (three or more spontaneous bleeds into a single joint within a consecutive 6-month period). A target joint is considered resolved when there are ≤2 bleeds into the joint within a 12-month period.

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

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

Definition of Bleed Types

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

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

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

Definition of Factor Replacement Regimens

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

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

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

Appendix 3. France Country-Specific Requirement

This appendix applies to study sites located in France.

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

1. GCP Training

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

2. SUSARs

Pursuant to a sponsor's safety reporting obligations under 21 Code of Federal Regulations (CFR) 312.32(c)(1), Pfizer will report to the investigator all Serious Unexpected Suspected Adverse Reactions ("SUSARs"). The investigator will receive and review SUSAR reports and report SUSARs to the responsible IRB/IEC according to institution's guidelines. Institution will retain SUSAR reports consistent with Section 11.2 of the Protocol.

Appendix 4. Turkey Country-Specific Requirement

Protocol Title

The original C0371004 study (hemophilia B cohort) was approved as an observational study in Turkey, as there was no intervention in the SoC factor replacement prophylaxis treatment and all the treatment decisions are taken by the investigators. This design is aligned with the requirements defined in the local Turkish regulatory "Guideline for Observational Drug Studies (13 November 2015)."[7] The study title was changed with protocol amendment 3 to include hemophilia A cohort and reference to subsequent Phase 3 studies, in order to clarify that the two lead-in study cohorts will participate in separate Phase 3 studies. Subsequently, on 11 November 2019, the Turkish MoH requested that the text regarding subsequent Phase 3 studies be deleted from the protocol title, as it is out of the scope of the objectives for the current study as defined in the regulatory guideline.

Protocol amendment 4, which reflects protocol changes specific to Turkey, removes the following text from the protocol title: *"Prior to the Respective Therapeutic Phase 3 Gene Therapy Studies."*

The protocol title for use specific to Turkey will be as follows:

- *"An open-label, non-investigational product, multi-center, lead-in study to evaluate prospective efficacy and selected safety data of current Factor IX (FIX) or Factor VIII (FVIII) prophylaxis replacement therapy in the usual care setting of moderately severe to severe adult hemophilia B participants (FIX:C≤2%) who are negative for neutralizing antibodies to adeno-associated virus vector-Spark100 (BENEGENE-1) and moderately severe to severe hemophilia A adult participants (FVIII:C≤1%) who are negative for neutralizing antibodies to adeno-associated virus vector 6 (AAV6)."*

Comprehensive study documents which apply to all countries, including the clinical study report and any protocol amendments, will include a description of the protocol title change for Turkey, but these documents will reflect the original study title. Shorter documents which apply to all countries, such as administrative letters, will not reflect the title change for Turkey but will reflect the original study title. Participant facing materials in Turkey will use the protocol title specific to Turkey.

Document Approval Record

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