Protocol C0371004

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

Statistical Analysis Plan
(SAP)

Version: 5

Date: 19-Sep-2024

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1. VERSION HISTORY

This statistical analysis plan (SAP) for study C0371004 is based on the protocol updates as described in the below table.

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
5.0/19 Sep 2024	8.0/31MAR2023	Protocol amendments, text accuracy, and statistical summary completeness and accuracy	Increased sample size for both cohorts to align with protocol amendments (Section 2.2). Updated text describing the algorithm used to count bleeds for ABR (Section 3.1). Updated text for nAb status endpoint for accuracy and removed the analysis combining both hemophilia A and B cohorts (Sections 3.3, 4.2, 5, 6.3.1). Removed text saying PA#5 and the corresponding analyses were only applicable to hemophilia B cohort. Updated Figure 2 and references to it to align with this change (Sections 4, 4.2, 4.4, 4.5, 6.1.1, 6.2.2). Added summary of prospective data for PA#5 analysis set (Section 6.1.1). Added clarifying text on reason for exclusion from efficacy analysis set (Section 4.2). Updated definition of safety analysis set (Section 4.3). Updated the name of the region 'Asia Pacific' to 'Asia' (Section 6.3.1). Added summary of follow-up duration (Section 6.5.2).
4.0/25 Mar 2021	5.0/01OCT2020	Summary method update	1. Added algorithms for defining treated bleeds (Section 3.1). 2. Updated summary method for ABR and AIR. 3. Added Section 6.7 COVID related outputs.
3.0/14Jan2021	5.0/01OCT2020	Protocol amendment	This SAP is updated to align with the protocol amendment 5 which increased sample size for participants with hemophilia B to support an additional cohort planned for the

			subsequent Phase 3 registration study.
2.0/17DEC2019	3.0/27JUN2019	Protocol amendment	This SAP is updated to align with the protocol amendment which includes an additional cohort (hemophilia A participants) as part of the 6-month lead-in study, to accelerate the initiation of the hemophilia A gene therapy phase 3 study.
1.0/20JUN2018	Original /23MAR2018	NA	NA

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C0371004. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

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

2.1. Study Objectives

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

• To establish prospective efficacy data of:
  • Factor IX (FIX) prophylaxis replacement therapy in the usual care setting of hemophilia B participants, who are negative for neutralizing antibody (nAb) to adeno-associated virus vector (AAV)-Spark100.
  • Factor VIII (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 and 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 population assessed (hemophilia B or hemophilia A participants).	• The frequency and percentage of nAb status to AAV-Spark100 and AAV6 (positive, negative).

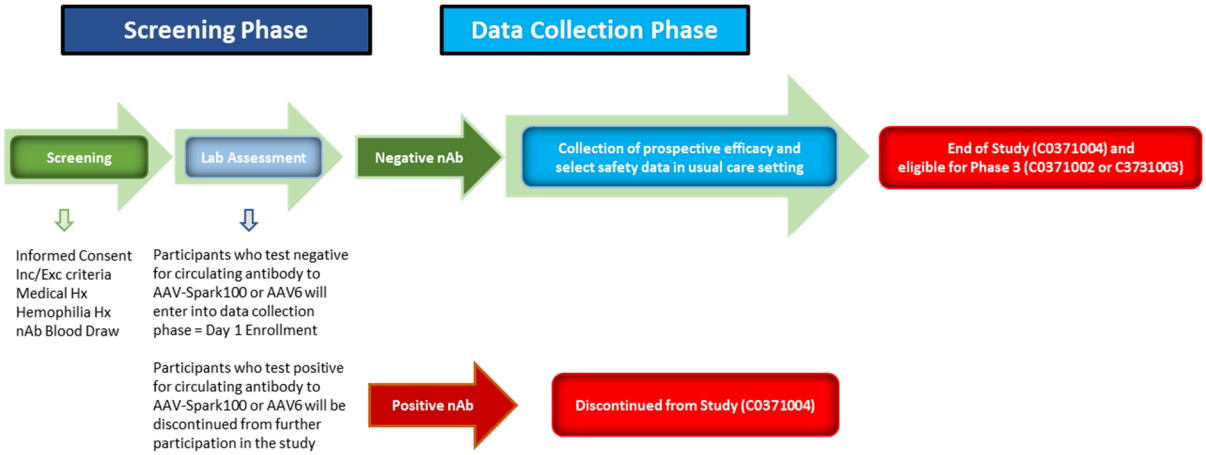
2.2. Study Design

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 (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, and moderately severe to severe adult hemophilia A participants (FVIII:C≤1%) who are negative for nAb to AAV6, prior to the subsequent Phase 3 gene therapy study C0371002 (hemophilia B) and C3731003 (hemophilia A) respectively. The study consists of two phases: the screening phase will include laboratory blood draw to determine nAb to either AAV-Spark100 or AAV6 in each respective group of participants (hemophilia B cohort and hemophilia A cohort) 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 and those hemophilia A participants who are below the established threshold for nAb to AAV6. The nAb-negative participants will be contacted to schedule a baseline visit to confirm eligibility, to issue their electronic infusion diary and continue on with the data collection phase. The baseline visit is defined as Day 1, which is the start of the prospective data collection phase. The duration of follow-up for participants

in this study (C0371004) will be at least 6 months until the respective thresholds of dosed participants are met. Subsequent to reaching the threshold in the dosing study, the duration of follow-up for participants recruited into this study (C0371004) will be dictated by the timing of their enrollment into the subsequent treatment protocol and may be less than 6 months. It is anticipated most participants will be followed for at least 6 months during the data collection phase, which is designed to provide prospective efficacy and selected safety data of FIX prophylaxis replacement therapy or FVIII prophylaxis replacement therapy in the usual care setting for hemophilia B and hemophilia A participants respectively. The participants of this lead-in study could subsequently participate in a dosing study of hemophilia B gene therapy of PF-06838435 or hemophilia A gene therapy of PF-07055480, if they properly complete this study and meet the inclusion/exclusion criteria for the subsequent trials.

The primary efficacy endpoint for C0371004 study will be annualized bleeding rate (ABR). The secondary efficacy endpoint will be annualized infusion rate (AIR). Additional secondary efficacy endpoints are factor consumption (dose and total) and number of bleeding events (spontaneous and/or traumatic). Primary and secondary endpoints will be evaluated separately in the respective hemophilia B and hemophilia A populations. The exploratory endpoint is the frequency of each nAb status (positive, negative) to AAV-Spark100 and to AAV6 in each of the respective populations assessed.

Figure 1. Study Schematic



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.

Participants withdrawn from the study or the subsequent treatment study may be replaced, at the discretion of the investigator and Sponsor (Pfizer, Inc).

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The primary endpoint is ABR (treated and total). A bleeding episode is defined in Protocol Appendix 2.

If a bleed is treated with FIX infusion (for Hemophillia B) or FVIII infusion (for Hemophilia A) (according to Bleeding eDiary or Bleeding CRF) within 72 hours post the start of bleeding (by comparing date/time of bleeding to date/time of infusion in Infusion eDiary or Infusion CRF), regardless of the type of treatment (preventive, prophylaxis or rescue medication), it will be considered as a treated bleed. If a bleed is not treated with FIX/FVIII infusion according to the Bleeding eDiary or the Bleeding CRF, the bleed will not be considered as a treated bleed but considered as an untreated bleed.

If there are multiple concurrent bleeds (spontaneous or traumatic) on the same date AND time but in different locations in a participant, they will be recorded as one bleed for that participant. If concurrent bleeds occurred on the same day but at different times and different locations, they will be counted as separate bleeds. Only new bleeds (as defined in Protocol Appendix 2) will be counted toward the number of bleeds for ABR calculation.

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

The ABR per participant based on prospectively collected bleeds will be calculated as:

The number of bleeds (all treated bleeding episodes including spontaneous and traumatic) x 365.25 days/number of days during the observation time period while the participant received prophylaxis factor replacement therapy in the usual care setting from baseline visit (Day 1) to end of study (date of study completion or discontinuation, whichever is earlier).

Number of bleeds (treated bleeds and all bleeds, respectively) and infusions within the last 12 months will be collected at the screening visit using hemophilia history CRF for all participants enrolled under Protocol Amendment 5 (01 Oct 2020) or under a subsequent protocol amendment. Thus the retrospectively collected ABR per participant will be equal to number of bleeds in the past 12 months collected in the Hemophilia History form. Participants enrolled in hemophilia A cohort or hemophilia B cohort prior to Protocol Amendment 5 will not have the CRF retrospectively filled out.

ABR combining retrospective and prospective data will be calculated as:

$$\frac{\text{(Number of bleeds from baseline visit (Day 1) to end of study + Number of bleeds collected in Hemophilia History form)}}{\text{(Number of days from baseline visit (Day 1) to end of study + 365.25)/365.25}}$$

3.2. Secondary Endpoint(s)

The AIR per participant will be calculated as:

The number of infusions received x 365.25 days/number of days during the observation time period while participant received prophylaxis factor replacement therapy in the usual care setting from baseline visit (Day 1) to end of study (date of study completion or discontinuation, whichever is earlier).

Similarly as ABR (Section 3.1), the retrospectively collected AIR per participant will be equal to number of infusions within the last 12 months collected in the Hemophilia History form.

AIR combining retrospective and prospective data will be calculated as:

$$\frac{\text{(Number of infusions from baseline visit (Day 1) to end of study + Number of infusions collected in Hemophilia History form)}}{\text{(Number of days from baseline visit (Day 1) to end of study + 365.25)/365.25}}$$

The annualized factor consumption will be calculated as:

The total factor replacement therapy consumption (in international unit [IU] and dose) x 365.25 days/number of days during the observation time period while the participant received factor prophylaxis replacement therapy in the usual care setting from baseline visit (Day 1) to end of study.

The number of bleeding episodes will be annualized using the same methods as the primary endpoint by spontaneous, traumatic and overall (treated and untreated) as defined in Protocol Appendix 2.

3.3. Exploratory Endpoint

For hemophilia B participants, AAV-Spark100 nAb status will be measured from the blood samples collected at the screening visit. For hemophilia A participants, AAV6 nAb status will be measured from the blood samples collected at the screening visit. The established threshold for AAV-Spark100 and AAV6 nAb status is 1:1 and 1:4, respectively.

3.4. Baseline Variables

Demographics, medical, surgical and hemophilia history (including the number of bleedings and infusions during the 12 months prior to enrollment, if collected) collected prior to the start of the prospective data collection will be summarized.

3.5. Safety Endpoints

3.5.1. Adverse Events

The adverse events (AE) reporting period in this study is defined as the time from the particpant's informed consent through end of study visit. Only SAEs, protocol defined AESI, and non-serious events leading to study discontinuation or unscheduled visits were reported; therefore, summaries of C0371004 will be restricted to these endpoints.

The events of special interest (ESI) include but are not limited to: inhibitor against FIX or FVIII, thrombotic events, and FIX or FVIII hypersensitivity reactions. The 3-tier AE approach will not be applied.

In this study, AE will not be defined as treatment emergent or not since this is a non-investigational drug study.

All AE data will be coded using the most updated version of MedDRA dictionary.

3.5.2. Laboratory Data

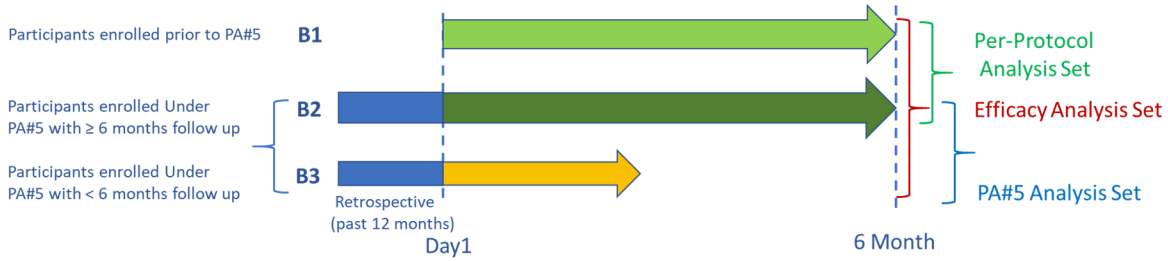
Laboratory data will not be reported as there are no safety laboratory measurements required during the prospective data collection phase of the protocol besides the procedures performed in the usual care setting.

4. ANALYSIS SETS

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population. There is no randomization or blinding in this study. The analysis population will be defined separately for the hemophilia B cohort and the hemophilia A cohort, unless otherwise specified.

The various follow-up periods for participants enrolled under Protocol Amendment 5 (PA#5) (or later) and prior to PA#5 are shown below in Figure 2.

Figure 2. Participants' follow-up scenarios



4.1. Full Analysis Set (Immunity Analysis Set)

The immunity analysis set is defined as all participants who signed an informed consent form (ICF) and had their blood sample collected and assayed for AAV-Spark100 or AAV6 immunity testing.

4.2. Efficacy Analysis Set

All participants in the full analysis set who were subsequently identified as nAb negative (negative for nAb to AAV-Spark100 for the hemophilia B cohort, or negative for nAb to AAV6 for the hemophilia A cohort), fulfilled the inclusion/exclusion criteria and who participated in the prospective data collection phase as part of their usual healthcare setting will be included in the efficacy analysis set (Groups B1, B2 and B3 in Figure 2).

Note: With regard to exclusion criterion 2 (Protocol Amendment 8, Section 4.2), any participant with more than 120 days of follow-up and for which the maximum number of days between 2 consecutive FVIII/FIX infusion records represents more than 25% of their follow-up duration will be considered non-compliant with documentation of bleeds and/or prophylaxis replacement therapy administration and will be excluded from the efficacy analysis set.

4.3. Safety Analysis Set

All enrolled participants (negative for nAb to AAV-Spark100 for the hemophilia B cohort, or negative for nAb to AAV6 for the hemophilia A cohort) who entered the prospective data collection phase will be included in the safety analysis set.

4.4. Per-Protocol Analysis Set

All efficacy analysis set participants who have completed at least 6 months of prospective data collection will be included in the per-protocol analysis set (Groups B1 and B2 in Figure 2).

4.5. Protocol Amendment 5 (PA#5) Analysis Set

All participants enrolled under Protocol Amendment 5 (PA#5) and afterwards, that fulfilled the inclusion/exclusion criteria and who had retrospective and prospective data collected will be included in the protocol amendment 5 analysis set (Groups B2 and B3 in Figure 2).
Of note, the Protocol Amendment 5 analysis set and analyses on retrospective data were originally intended to be applicable to the hemophilia B cohort only, as the hemophilia A cohort had closed enrollment by the time of Protocol Amendment 5 implementation. However, enrollment for the hemophilia A cohort was re-opened in July 2022 to account for attrition following the 1-year temporary halt in Study C3731003 and retrospective data were collected for the newly enrolled hemophilia A participants.

5. GENERAL METHODOLOGY AND CONVENTIONS

The final analysis of each cohort will be performed after the last enrolled participant of the respective cohort completes his end of study visit. The nAb status of AAV-Spark100 and AAV6 endpoints will be evaluated for the hemophilia B and hemophilia A cohorts, respectively. A summary of nAb status of AAV-Spark100 for the hemophilia B cohort will be provided after the last participant's visit within this cohort. A summary of nAb status of AAV6 for the hemophilia A cohort will be provided when all participants from this cohort complete their end of study visit. In addition, when the subsequent study C0371002 or C3731003 reaches an interim analysis timepoint, the data obtained from the appropriate cohort of this study will be used as baseline data for that interim analysis. This may potentially occur earlier than the final analysis for each cohort and/or this study.

The data will be presented separately for each cohort, unless otherwise specified.

5.1. Hypotheses and Decision Rules

There is no hypothesis test planned for this study. Data are collected to facilitate a comparison with post gene therapy efficacy in the subsequent treatment studies (C0371002 or C3731003).

5.2. General Methods

Descriptive statistics will be displayed to summarize data collected in this study. Demographics will be also summarized by region. For numeric variables, the summary statistics include n, mean, standard deviation, median, Q1, Q3, minimum, maximum. For categorical variables, the summary statistics include count and percent of the categories.

5.3. Methods to Manage Missing Data

There is no missing data expected for nAb antibody status, since each participant in the immunity analysis set will have a nAb status reported as defined in Section 4.1.

Missing data for endpoints such as ABR, AIR, total consumption of replacement factor will not be imputed for data summaries or listings. No statistical inference will be made.

For the analysis of safety endpoints, no missing data will be imputed unless otherwise specified.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Annualized Bleeding Rate

The primary endpoint listed in the protocol is the annualized bleeding rate (ABR; treated and total).

ABR during the prospective data collection period
Annualized bleeding rate during the prospective data collection period will be summarized using descriptive statistics (ie, n, mean, standard deviation, median, Q1, Q3, minimum, maximum) by cohort. The ABR will be summarized for the efficacy analysis set, the per-protocol analysis set, and the PA#5 analysis set.

ABR during the retrospective data collection period
Annualized bleeding rate during the retrospective data collection period will be summarized using descriptive statistics. The ABR will be summarized for the PA#5 analysis set.

ABR from the combined the retrospective and prospective data collection period
Annualized bleeding rate from the combined retrospective and prospective data collection period will be summarized using descriptive statistics. The ABR will be summarized for the PA#5 analysis set.

ABR will be listed in a data listing. For retrospectively collected data, the source of collection (medical records, diary log, or participant recall) will be presented.

The analyses will be provided for ABR of treated bleeds and ABR of all bleeds, respectively.

6.2. Secondary Endpoint(s)

6.2.1. Annualized Infusion Rate and Annualized Total Factor Replacement Therapy Consumption

Both AIR and annualized total factor replacement therapy consumption will be summarized using descriptive statistics. The AIR data will be summarized similarly as ABR as described in Section 6.1.1.

6.2.2. Specific Type of Bleeding Episodes

ABR of bleeding episodes of specific type will be summarized using descriptive statistics by cohort. Bleeding type is not available in retrospective data collection. Thus, the ABR of bleeding episodes of specific type will be summarized for prospectively collected data only. The summary will be presented for the efficacy analysis set and the per-protocol analysis set.

6.3. Other Endpoint(s)

6.3.1. Analysis of nAb Status

AAV-Spark100 nAb status and AAV6 nAb status will be measured from the blood samples collected at the screening visit. NAb status will be summarized as a binary endpoint in a summary table. Additionally, exploratory nAb titers (continuous data) will be included in an individual listing, along with the nAb status.

All participants from the full analysis set (immunity analysis set) will be included in this analysis.

The individual AAV-Spark100 nAb titer will be listed along with the AAV-Spark100 nAb status for each hemophilia B participant by region (Asia, Australia, Europe, Middle East, North America, South America). The study sites included in each region will be finalized after the site selection/participant enrollment decisions are made.

The individual AAV6 nAb titer will be listed along with the AAV6 nAb status for each hemophilia A participant by region. The study sites included in each region will be finalized after the site selection/participant enrollment decisions are made.

The AAV nAb status will be summarized using frequency and percentage by nAb status (positive, negative) overall for all countries combined, and by region. The point estimates of AAV-Spark100 nAb and AAV6 nAb positive rate and the 2-sided 95% confidence intervals (CI) will be provided overall for all countries combined and by region using the exact Clopper-Pearson method. The summary will include the number of nAb positive participants and the number of sampled participants. The nAb status of AAV-Spark100 will be summarized for the hemophilia B cohort and the nAb status of AAV6 will be summarized for the hemophilia A cohort.

6.4. Subset Analyses

No sub-group analyses are planned.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Demographics, medical, surgical and hemophilia history will be summarized using descriptive statistics separately for each cohort. Summaries will be provided overall and by analysis set (safety analysis set, efficacy analysis set, per-protocol analysis set, PA#5 analysis set, respectively). Prior factor (factor IX or factor VIII) treatment will be collected under prior/concomitant medications. These data will be reported in subject-level listings for participants enrolled in the study.

Hemophilia history, including patient exposure categories, disease severity, target joints, current treatment regimen and the type of factor mutation (if known), will be categorically summarized using frequency and percentage for all countries.

6.5.2. Study Conduct and Participant Disposition

Participant evaluation groups will be summarized by end of study participant disposition and by analysis set separately for each cohort (ie, immunity analysis set, safety analysis set, efficacy analysis set, per-protocol analysis set and PA#5 analysis set). Frequency counts will be supplied for participant discontinuation(s) for all countries combined and by region.

A summary of follow-up duration in this study will be provided separately for participants with <180 days of follow-up, participants with ≥180 days of follow-up, and overall, by analysis set (safety analysis set and efficacy analysis set). Additionally, the number and percentage of participants with a follow-up duration of 1 year or more will be provided.

6.5.3. Study Treatment Exposure

No investigational study treatment is planned in this protocol.

6.5.4. Concomitant Medications and Non-Drug Treatments

Exposure to standard of care data is collected in concomitant medication CRF. Concomitant and other non-drug treatments will be coded with WHO Drug dictionary and presented in summary table.

6.6. Safety Summaries and Analyses

6.6.1. Adverse Events

The AE reporting period in this study is defined 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.

The events of special interest include but are not limited to FIX/FVIII inhibitor, thrombotic events, and FIX/FVIII hypersensitivity reactions. Frequency and percentage of these ESI events will be summarized by event. In addition, serious adverse events, and any events leading to discontinuation from the study will also be summarized.

Safety data collected from those participants that sign the informed consent document and subsequently are screen failed will be listed-and presented separately.

The AE data will be coded using MedDRA dictionary and be summarized in tables by system organ class (SOC) and preferred term (PT).

6.7. COVID-19 Related Data Listings and Summaries

The impact of Coronavirus disease 2019 (COVID-19) on C0371004 is expected to be minimal. Since no investigational product will be administered during the study, there should be no treatment discontinuations. Additionally, given the mechanism of data collection for key endpoints (ie, eDiary to capture bleeding and infusion information and all other data are collected via phone calls), missing data due to COVID-19 is expected to be

minimal. Additionally, it is not anticipated that participants would discontinue from the study due to COVID-19. To confirm that COVID-19 has not impacted the trial, the following data listings and summaries will be provided.

- Study disruption/discontinuation due to COVID-19 will be listed, and a description of how the individual's participation was altered will be provided.
- Protocol Deviations related to COVID-19 will be listed.
- COVID-19 related Adverse Events will be summarized by SOC and PT, and will also be listed.
- Any study discontinuation due to COVID-19 related AE, SAE or death related to COVID-19 will be listed.

7. INTERIM ANALYSES

There is currently no plan for a formal interim analysis. However, periodic reviews will be conducted to provide an assessment of AAV-Spark100 and AAV6 nAb status, efficacy and safety summaries for the purpose of publication (eg, abstracts, manuscripts) or regulatory submission and responses. The review will be planned once the target number of participants have been enrolled into the data collection phase. These reviews and summaries will include but may not be limited to the frequency of participants who are positive and negative for neutralizing antibodies against AAV-Spark100 and AAV6, distribution of the population, range of neutralizing antibody titers, ABR, AIR, annualized total factor replacement therapy consumption, AE, and other screening data related to hemophilia, such as hemophilia history.

The final analysis of each cohort will be performed after the last enrolled participant of the respective cohort completes his end of study visit. Separate CSR will be generated for hemophilia A and hemophilia B cohorts, respectively.

8. APPENDICES

List of abbreviations

Abbreviation	Term
AAV6	adeno-associated virus 6
AAV-Spark100	Bioengineered AAV capsid, derived from a naturally occurring AAV serotype
ABR	annualized bleeding rate
AIR	annualize infusion rate
AE	adverse event
AESI	adverse events of special interest
CI	confidence interval
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
ESI	events of special interest
FIX	Factor IX
FIX:C	Factor IX circulating
FVIII	Factor VIII
ICF	informed consent form
IgG	Immunoglobulin G
MedDRA	Medical Dictionary for Regulatory Activities
nAb	neutralizing antibodies
PT	Preferred Term
Q1	first quartile
Q3	third quartile
SAE	serious adverse events
SAP	statistical analysis plan
SOC	System Organ Class