NCT #: NCT03734588

DESCRIPTIVE STATISTICAL ANALYSES SUPPORTING

aCSR of SPK-8016-101

Protocol: SPK-8016-101

Dose-Finding Study of SPK-8016 Gene Therapy in Patients With Hemophilia A to Support Future Evaluations in Individuals With FVIII Inhibitors

Protocol:	SPK-8016-101
Protocol Version:	Version 3.0
Date of Protocol:	19 March 2021

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LIST OF ABBREVIATIONS

AAV	Adeno-associated virus
ABR	Annualized bleeding rate
AE	Adverse event
AIR	Annualized infusion rate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BDD	B-domain-deleted
BUN	Blood urea nitrogen
BQL	Below quantifiable limits
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
EFF FUP	Efficacy follow-up
ELISpot	Enzyme-linked immunospot assay
EOS	End-of-study
EQ-5D-5L	Euro quality-of-life five dimensions questionnaire
FAS	Full analysis set
FVIII	Coagulation factor VIII
FVIII:C	Factor VIII in circulation
GGT	Gamma-glutamyl transferase
HLA	Human leukocyte antigen
LDH	Lactate dehydrogenase
mITT	Modified Intention to Treat
PBMC	Peripheral blood mononuclear cells
PK	Pharmacokinetics
RBC	Red blood cell
SAE	Serious treatment-emergent adverse event
SD	Standard deviation
SOC	System organ class

SPK-8016	Study drug in this protocol [redacted]
TEAE	Treatment-emergent adverse event
WBC	White blood cell

1. INTRODUCTION

SPK-8016 is an investigational adeno-associated virus (AAV) gene therapy medicinal product. SPK-8016 was being developed by Spark Therapeutics for the treatment of hemophilia A, a deficiency of blood coagulation factor VIII (FVIII) that is an inherited X-linked recessive mutation carried by females and expressed mainly by males, affecting approximately 1 in 4,000 male births. The severity of hemophilia A is characterized by the endogenous level of FVIII measured in plasma.

This document describes the analyses that support the aCSR for study SPK-8016-101 based on protocol SPK-8016-101 Amendment 2, Version 3.0 dated 09-Feb-2021.

1.1. STUDY OBJECTIVES REPORTED IN THE aCSR

1.1.1. PRIMARY OBJECTIVES REPORTED IN THE aCSR

- To evaluate the safety and tolerability of SPK-8016.
- To evaluate the efficacy as evidenced by prevention of bleeds and level of FVIII expression with SPK-8016.

1.1.2. SECONDARY OBJECTIVES REPORTED IN THE aCSR

- To evaluate additional parameters associated with SPK-8016 directed FVIII expression.
- To characterize the immune response to the transgene product.

1.2. ENDPOINTS REPORTED IN THE aCSR

1.2.1. EFFICACY ENDPOINTS

- Annualized bleeding rate (ABR) post-SPK-8016 infusion
- Annualized FVIII infusion rate (AIR) post-SPK-8016 infusion

1.2.2. PHARMACOKINETICS ENDPOINTS

- Peak FVIII activity
- Median FVIII activity from weeks 40 through 52 post-SPK-8016 infusion

1.2.3. SAFETY ENDPOINTS

For safety and tolerability:

- Exposure of immunomodulatory treatment
- Adverse events (SPK-8016 related and immunomodulation-related)
- Clinical laboratory evaluation

1.3. STUDY DESIGN

This is a Phase 1/2a, open-label, non-randomized, dose escalation study to evaluate the safety, tolerability, and efficacy of a single IV infusion of SPK-8016 in men with clinically severe hemophilia A, and no measurable inhibitor against FVIII.

1.3.1. STATISTICAL HYPOTHESES

No statistical hypotheses will be tested as part of this protocol. This study will be used to establish an initial safety and efficacy profile of SPK-8016.

2. ANALYSIS POPULATIONS

The Full Analysis Set (FAS) is defined as all participants who receive the infusion of SPK-8016. The analyses of the described endpoints will be performed in this population.

3. STATISTICAL ANALYSES SUPPORTING THE aCSR

3.1. GENERAL CONSIDERATIONS

Unless otherwise specified, continuous variables will be summarized by the following descriptive statistics: number of observations, mean, median, standard deviation, minimum, and maximum. Categorical variables will be presented with the number and percentage in each category.

3.2. ANALYSIS OF EFFICACY

3.2.1. ANNUALIZED BLEEDING RATE (ABR)

ABR following SPK-8016 administration and beginning 28 days following SPK-8016 administration will be listed by participant. Bleeds will be categorized and analyzed using the following definitions:

Bleed Type	Description
All Bleeds	This will be comprised of both treated and non-treated bleeds, except when the bleed is a result of a surgery or procedure, including cosmetic (ie. Tattoos) or dental procedures.
Treated Bleeds	A bleed is considered to be a "treated bleed" if it is reported on the eCRF as being treated with Factor VIII and is not a result of a surgery or procedure. This category will only be summarized for bleeding events post-SPK-8016 administration, due to the limitation of baseline bleeding rates.
Spontaneous Bleeds	A bleed is considered to be a "spontaneous bleed" if it is reported on the eCRF as being spontaneous.
All Joint Bleeds	This will be comprised of both treated and non-treated bleeds in a joint as specified in the eCRF and not a result of a surgery or procedure. This category will only be summarized for bleeding events post-SPK-8011 administration, due to the limitation of baseline bleeding rates.

ABR Calculation Rules:

3 Day Rule: Two or more bleeds of the same type (e.g., "joint," "muscle," or "other") and at the same anatomical location are considered one bleed if the second occurs within 72 hours from the last treatment for the first bleed. The last treatment is defined as the last treatment before a new bleed occurs, either in the same or in a different location.

Censoring Rule: If a participant loses transgene derived FVIII, the duration of follow-up time for calculation of ABR will be censored on the day in which the central lab one-stage FVIII activity level falls to equal or below diagnostic historical value 28 days or later following SPK-8016 infusion. FVIII activity level equal or below diagnostic historical value is considered as complete loss of expression.

ABR Calculation Formula:

ABR post 28 days will be computed as:

$$ABR28 = \frac{365.25 * observed\ number\ of\ bleeding\ events}{EFF\ FUP\ (in\ days) - 28}$$

rounded to the tenth place.

ABR post day 0 will be computed as:

$$ABR = \frac{365.25 * observed\ number\ of\ bleeding\ events}{EFF\ FUP\ (in\ days)}$$

rounded to the tenth place. EFF FUP, the duration of efficacy follow-up.

3.2.2. ANNUALIZED INFUSION RATE (AIR)

AIR following SPK-8016 administration and beginning 28 days following SPK-8016 administration will be listed by participant. Two main types of infusions were reported: "all infusions" and "infusions to treat bleeds". The number of recorded FVIII infusion events will be categorized and analyzed using these two main categories of infusions. The reported infusions during the prior 52-week hemophilia history were "all infusions" only.

AIR Calculation Rules:

Censoring Rule: If a participant loses transgene derived FVIII, the duration of follow-up time for calculation of AIR will be censored on the day in which the central lab one-stage FVIII activity level falls to equal or below diagnostic historical value 28 days or later following SPK-8016 infusion.

AIR Calculation Formula:

AIR post 28 days will be calculated as follows:

$$AIR28 = \frac{365.25 * observed\ number\ of\ FVIII\ infusions}{EFF\ FUP\ (in\ days) - 28}$$

rounded to the nearest integer.

AIR post day0 will be calculated as follows:

$$AIR = \frac{365.25 * observed\ number\ of\ FVIII\ infusions}{EFF\ FUP\ (in\ days)}$$

rounded to the nearest integer. EFF FUP, the duration of efficacy follow-up.

Change in AIR and AIR28 will only be calculated for the number of recorded "all infusions" because only all infusions are collected for the prior to gene therapy period.

Change in AIR will be calculated as:

$$Change\ in\ AIR = Post\ Infusion\ AIR - \ Baseline\ AIR$$

Change in AIR28 will be calculated as:

$$Change\ in\ AIR28 = Post\ Infusion\ AIR28 - \ Baseline\ AIR$$

3.3. PHARMACOKINETICS ANALYSIS

FVIII:C activity level (one stage; central lab-recorded) following SPK-8016 administration will be listed by participant.

3.3.1. PEAK FVIII ACTIVITY

The peak FVIII:C activity level and the time to the peak will be computed for each participant.

3.3.2. MEDIAN FVIII ACTIVITY

Median FVIII activity from weeks 40 through 52 post-SPK-8016 infusion will be calculated by participant.

3.4. ANALYSIS OF SAFETY

3.4.1. CONCOMITANT IMMUNOMODULATORY TREATMENT

The frequency and duration of use of concomitant immunosuppressant medications will be listed for individual participant and summarized by ATC pharmacologic class. "Concomitant" is defined as any intervention with a start date on or after the date of SPK-8016 administration. The combinations of medications will be considered in the reports. The duration of individual or combinations of immunosuppressant medication will exclude the interruptions between the dosing changes.

3.4.2. ADVERSE EVENTS

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) with an onset date on or following SPK-8016 administration. The number, frequency and severity of AEs, TEAEs and serious treatment-emergent adverse events (TESAEs) will be categorized and analyzed by all events, events related to SPK-8016 or Immunomodulation agents. All summaries will be classified by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, by MedDRA version 24.0 system organ class (SOC) and preferred term. TEAEs will be also classified by maximum severity.

3.4.3. CLINICAL LABORATORY ANALYSIS

Clinical laboratory data (central lab-recorded, and local lab when available) for individual participant will be listed for actual values by each visit, including clinical chemistry, hematology, urinalysis, liver function tests, and coagulation parameters. Clinical laboratory values above or below the normal range will be flagged. The clinical laboratory data will include:

Clinical chemistry: carbon dioxide, chloride, cholesterol, serum creatinine, HDL cholesterol, LDL cholesterol, phosphate, potassium, protein, sodium, triglycerides, blood urea nitrogen (BNU), and VLDL cholesterol.

Hematology: white blood cell (WBC) count with differential (basophils, eosinophils, Erythrocytes, neutrophils, lymphocytes, monocytes); red blood cell (RBC) count (hemoglobin, hematocrit, platelet count).

Urinalysis: glucose, ketones, occult blood, protein, pH.

Liver function tests: alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, gamma-glutamyltransferase (GGT), glucose, haptoglobin, indirect bilirubin, lactate dehydrogenase (LDH), total protein.

Coagulation: activated partial thromboplastin time (aPTT), FVIII activity CSA (%), FVIII activity clotting (%), FVIII activity OSA (%), FVIII antigen, FVIII inhibitor, Peak Factor VIII Activity OSA (%), Von Willebrand Factor (%), Von Willebrand Factor Activity (%).

3.4.4. NEUTRALIZING ANTIBODY ANALYSIS

The neutralizing antibodies (NAbs) against the AAV capsid post-SPK-8016 infusion will be listed for individual participant by visit.

3.5. INTERIM ANALYSIS

No interim analysis will be performed for this study.

3.6. MISSING DATA/IMPUTATION

Imputation will not be performed for any missing data.

3.7. VISITS AND VISIT WINDOWS

3.7.1. DEFINITION OF BASELINE

The diagnostic historical FVIII activity level, based on historical medical records and captured in the CRF, will be used as baseline FVIII activity. Baseline bleeding and infusion rates are historical as well, collected as the number of bleeding or infusion events in the prior 52 weeks.

For all other assessments, baseline is defined as the last assessment prior to the start of SPK-8016 infusion. Unless otherwise specified, data will be analyzed according to nominal study visits.

3.7.2. DAYS TO ONSET OF EVENTS

For efficacy assessments, including bleeding events, FVIII:C activity levels and other laboratory data, and safety assessments of adverse events and concomitant medications/procedures days of follow-up and days to onset of the event/medication/procedure from administration of SPK-8016 will be calculated as:

Days to onset of events = (study visit or assessment date) – (SPK-8016 infusion date).

This preserves the protocol-specified nomenclature for a Day 0 record on the study data base.

3.7.3. DURATION OF EVENTS

Duration of an adverse event or period of use of procedure will be defined as:

Duration of events = stop date - start date + 1.

This allows for a minimum duration of one day.

The duration of individual or combinations of concomitant medications will exclude the interruptions between the dosing changes.

3.8. PARTICIPANT DISPOSITION

The number of participants screened and the number of participants not eligible for the study (overall and categorized by reason: consent withdrawal, screen-failure, screened but not enrolled and other) will be presented. Safety and efficacy follow-up time will be calculated for each participant.

Safety follow-up time in days will be calculated as:

SAF FUP = (lesser of date of study withdrawal or date of last contact) - SPK-8016 infusion date + 1

Efficacy follow-up time in days will be calculated as:

EFF FUP = (lesser of date of study withdrawal, date of last contact or date of efficacy censoring) - SPK-8016 infusion date + 1

Follow-up time will also be displayed in weeks by dividing the days of follow-up by 7 and summarized.

3.9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The following characteristics will be listed by participant:

3.9.1. BASELINE AND DEMOGRAPHIC CHARACTERISTICS

- Demographics: Age, sex, race, ethnicity, height, weight, and body mass index (BMI).
- Serology: HBV antibody, HCV antibody, and HIV antibody.
- FVIII Treatment History: FVIII therapy type.

3.9.2. HEMOPHILIA HISTORY

- Hemophilia History: FVIII level (<1%, 1-2%), FVIII genotype, human leukocyte antigen (HLA) genotype, recent FVIII inhibitor value (BU), historical allergic anaphylaxis reactions, number of spontaneous bleeds in past 52 weeks, number of traumatic bleeds in past 52 weeks.

3.9.3. MEDICAL HISTORY AND CURRENT MEDICAL CONDITIONS

Coded terms of medical, surgical and vaccine history will be listed by participant.

3.9.4. PRIOR MEDICATION

Prior medications will be summarized by ATC classification and product name preferred term by participant. Prior medications are those which have a start date prior to SPK-8016 infusion date.

4. LIST OF TABLES AND LISTINGS

A table contents of tables and listings will be presented in an appendix to this document.