STATISTICAL ANALYSIS PLAN

Protocol: SPK-8011-101, SPK-8011/8016-LTFU
Gene-transfer, open-label, dose-escalation study of SPK-8011 [adeno-associated viral vector with B-domain deleted human factor VIII gene] in individuals with hemophilia A

Protocol:	SPK-8011-101 Version 8.0 Amendment 7, SPK-8011/8016-LTFU Amendment 2
SAP Version:	**v1.0**
SAP Date:	08 March 2024

DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
Final 1.0	08 MAR 2024

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
	N/A	Initial release	N/A

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AAV	Adeno-associated virus vector
AAV2	Adeno-associated virus vector, serotype 2
AAV8	Adeno-associated virus vector, serotype 8
AAVSpark100	Adeno-associated virus Spark100 vector
ABR	Annualized bleeding rate
AE	Adverse event
AESI	Adverse event of special interest
AIR	Annualized infusion rate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BDD	B-domain-deleted
BMI	Body mass index
BUN	Blood urea nitrogen
BQL	Below quantifiable limits
CI	Confidence interval
CSA	Chromogenic Assay
DMC	Data Monitoring Committee
eCRF	Electronic case report form
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
hFVIII	Human coagulation factor VIII
HJHS	Hemophilia joint health score
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonisation
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
OSA	One-Stage Assay
PBMC	Peripheral blood mononuclear cells
PK	Pharmacokinetics
QoL	Quality of life
rAAV	Recombinant factor VIII
RBC	Red blood cell

SAE	Serious treatment-emergent adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell

1. INTRODUCTION

SPK-8011, an investigational gene transfer medicinal product, is a recombinant adeno-associated viral (rAAV) vector that contains a bioengineered capsid (AAV-Spark200) and a codon optimized expression cassette to drive expression of human coagulation factor VIII (FVIII). SPK-8011 is being developed by Spark Therapeutics for the treatment of hemophilia A. *The Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products* and findings from previous clinical studies with AAV2, AAV8 and AAVSpark100 vectors were considered in the development of this Statistical Analysis Plan (SAP). In addition, the recently issued (January 2020) *FDA Draft Guidance for Industry: Human Gene Therapy for Hemophilia* provides a framework for definition and evaluation of clinical endpoints to be further investigated in a planned Phase 3 clinical development program.

This SAP contains descriptions of analyses for protocol SPK-8011-101 Amendment 7, Version 8.0 dated 09-Feb-2021 and protocol SPK-8011/8016-LTFU Amendment 2 dated 02 Feb 2023. This SAP will include analyses that require data from both the SPK-8011-101 and SPK-8011/8016-LTFU studies. Data will be integrated prior to analysis. The planned methods of analyses are consistent with the International Conference on Harmonisation (ICH) E9 Guidance (Statistical Principles for Clinical Trials). When discrepancies exist between the descriptions provided in the study protocols and the SAP, the SAP takes precedence. This includes provisions in the SAP for more detailed definitions of certain endpoints, mathematical constructs (including imputation methodology, if so stated) and specification of the way analyses will be undertaken (e.g., continuous-based, qualitative, change from baseline).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary study objectives for Protocol SPK-8011-101 are:

- To evaluate the safety and tolerability of SPK-8011
- To evaluate the efficacy of SPK-8011

The primary study objectives for Protocol SPK-8011/8016-LTFU are:

- To evaluate the long-term safety of SPK-8011 and SPK-8016
- To evaluate the long-term efficacy of SPK-8011 and SPK-8016

2.2. Secondary Objectives

The secondary study objectives for Protocol SPK-8011-101 are:

- To determine the pharmacokinetic (PK) characteristics of SPK-8011
- To characterize the immune response to the vector and transgene product

The secondary study objectives for Protocol SPK-8011/8016-LTFU are:

- To further characterize the effect of SPK-8011 and SPK-8016 on the participant's QoL and health-economics outcomes

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The primary endpoints for Protocol SPK-8011-101 are:

For safety and tolerability:

- Clinically notable changes from baseline in physical examinations and vital signs
- Incidence of adverse events, including clinically significant abnormal laboratory values
- Hepatic transaminase elevations requiring immunosuppression

For efficacy:

- Primary PK parameters of peak and steady-state FVIII activity levels assessed by coagulation clotting assays
- Number of FVIII infusions after vector administration
- Number of bleeding events (spontaneous and traumatic) after vector administration

The primary endpoints for Protocol SPK-8011/8016-LTFU are:

For safety:

- Incidence of FVIII inhibitors
- Incidence of all AEs
- Incidence(s) of new or exacerbation of adverse events of special interest (AESIs): malignancies, neurologic, rheumatologic or other autoimmune, hepatic or hematologic disorders

For efficacy:

- Annual bleeding rate (ie, number of bleeding events).
- Factor VIII activity levels

- Total FVIII consumption
- Number of FVIII infusions

3.2. Secondary Endpoints

The secondary endpoints for Protocol SPK-8011-101 are:

Additional PK assessments will include, but are not limited to:

- Time to achieve steady-state FVIII activity level
- Peak FVIII activity summary; time to peak FVIII activity
- Peak ALT summary; time to peak ALT
- Vector-shedding of SPK-8011 in bodily fluids

Incidence of immune responses to AAV capsid protein and B-domain-deleted human FVIII (BDD-hFVIII) transgene

The secondary endpoints for Protocol SPK-8011/8016-LTFU are:

Joint health assessments

- Target Joint Assessment (including arthropathy assessment)
- Hemophilia Joint Health Score (HJHS) version 2.1

QoL assessments

- Haem-A-QoL Questionnaire
- EuroQol 5 Dimension 5 Level (EQ-5D-5L)

Activities assessments

- Hemophilia Activities List (HAL) Questionnaire

Health Economics Assessment, including, but not limited to, the following:

- Number of unplanned hospitalizations
- Number of hospitalization (inpatient) days
- Number of emergency room (urgent care) visits
- Number of physician (office or clinic) visits, excluding study visits
- Number of days of work/school missed

3.3. Exploratory Endpoints

The exploratory endpoints for Protocol SPK-8011-101 are:

Joint assessments:

- Number of target joints
- Hemophilia Joint Health Score

Activities assessments:

- Hemophilia Activities List
- Change in Level of Activity questionnaire

Quality-of-life (QoL) assessments:

- Haem-A-QoL questionnaire
- Euro Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) questionnaire

Health-economic parameters to include, but are not limited to, collection of information on the following:

- Number of hospitalizations (excluding pre-planned hospitalizations documented at screening)
- Number of hospitalization days
- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of days off from school or work

ELISpot immune profiling

Other exploratory inflammatory profiling of plasma and immune function gene expression of peripheral blood mononuclear cells (PBMCs) after vector administration (exploratory biomarkers) will be assessed and analyzed separately and that analysis is outside of the scope of this SAP.

4. STUDY DESIGN

Study SPK-8011-101 is a Phase 1/2a, open-label, non-randomized, dose escalation study to evaluate the safety, tolerability, and efficacy of a single intravenous (IV) infusion of SPK-8011 in men with severe hemophilia A. Up to 50 eligible participants will be dosed with a single IV infusion of SPK-8011.

Study SPK-8011/8016-LTFU is a multi-center, LTFU study in males with hemophilia A who have received a single intravenous administration of SPK-8011 or SPK-8016 in and rolled over from studies SPK-8011-101 and SPK-8016-101 respectively.

4.1. Sample Size Determination

The sample size is based on the need to establish the initial safety and efficacy profile of SPK-8011. Up to 50 eligible participants are planned to be dosed.

The sample size is based on clinical, rather than statistical considerations.

4.2. Statistical Hypotheses

No formal statistical hypotheses will be tested. This analysis will be used to establish and characterize an initial safety and efficacy profile of SPK-8011.

5. STATISTICAL ANALYSIS

5.1. Analysis Populations

The Full Analysis Set (FAS) is defined as all participants who receive an infusion of SPK-8011. The Safety Population is defined as all participants who receive any study-mandated medication.

The analyses of safety and exploratory efficacy will be performed in the FAS population, unless otherwise specified, within SPK-8011 dose groups or overall. In the event that the FAS and Safety Population are identical, the Safety Population will not be used for any analyses.

5.2. Subgroups

The subgroups of interest are the dose groups and the participants previously on prophylactic FVIII therapy and on-demand therapy. Additional subgroups of interest such as HIV status might be explored.

5.3. Treatment Assignment

Analysis will be done according to planned dose for participants in the study. Summary tables will be presented by SPK-8011 dose group (and overall), and prior FVIII regimen (prophylaxis vs. on-demand), unless specified otherwise. For summary tables and figures, data will be presented according to the following SPK-8011 dose groups:

- $5x10^{11}$ vg/kg
- $1x10^{12}$ vg/kg
- $2x10^{12}$ vg/kg
- $1.5x10^{12}$ vg/kg

All subjects in the $1.5x10^{12}$ vg/kg dose will be presented together, regardless of the immunoprophylactic regimen used. Patient listings will be presented using the following dose groups:

- $5x10^{11}$ vg/kg
- $1x10^{12}$ vg/kg
- $2x10^{12}$ vg/kg
- $1.5x10^{12}$ vg/kg
- $1.5x10^{12}$ vg/kg + MMF
- $1.5x10^{12}$ vg/kg + TCZ

5.4. General Considerations

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

Information collected in the electronic case report form (eCRF) and available in electronic data transfers will be listed.

Subject IDs recorded in the EDC will be used for each data listing. Subject IDs from SPK-8011/8016-LTFU will be mapped to the subject IDs in study SPK-8011-101 using the subject enrollment dataset in the SPK-8011/8016-LTFU database. All listings will utilize the Subject IDs from study SPK-8011-101. The data collected in SPK-8011-101 at the Week 52/End of Study (EOS) visit is the same data that is collected in SPK-8011/8016-LTFU at the Day 1 visit. To eliminate duplicate data when integrating the two databases for analysis, the Day 1 visit from SPK-8011-8016-LTFU will be removed from the integrated datasets.

5.5. Key Definitions

5.5.1. Baseline

The diagnostic historical FVIII activity level, based on historical medical records and captured in the CRF, will be used as a participant's baseline FVIII activity. Baseline bleeding and infusion rates are historical as well and are 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-8011 infusion.

5.5.2. Study Days

For efficacy assessments, including bleeding events, FVIII:C activity levels and other laboratory data, and safety assessments of adverse events and concomitant medications/procedures, chronological days to onset of an event/medication/procedure from administration of SPK-8011 will be calculated as:

assessment date – SPK-8011 infusion date.

This preserves the protocol-specified nomenclature for a Day 0 (pre-dose or post-dose) record on the study database.

Durations of adverse events or concomitant medications/procedures will be defined as:

stop date - start date + 1.

This allows for a minimum duration of one day.

5.6. Missing Data Conventions

The following approach will be used for imputing partial prior/concomitant medication and adverse event dates with missing days:

- for partially missing start dates: assign “01” as the day.
- for partially missing end dates: assign last day of the month as the day.

Missing days or months should be reported as UN and UNK on listings. Missing months or years will not be imputed. If year is entered as ‘0000’, this will be considered missing.

For purposes of summarization, i.e. for all uses of such data except listings, FVIII activity values below the lower limit of quantifiability (LLOQ) will be set to 0.5 x LLOQ. That is, if a result is given as “<X.XX”, values will be set to X.XX. This imputation method will not apply to diagnostic historical FVIII activity, but rather the upper bound of the range will be used instead.

In the event of missing or incomplete dates for bleeds or infusions, if the event is recorded in the LTFU study, the date will be imputed to occur after SPK-8011 infusion for the purposes of counting events and computing annualized rates. In the event such a participant is censored using the censoring rules in Section 5.7, the bleed will be assumed to occur prior to the censoring date unless sufficient information is given to indicate the bleed occurred after censoring (e.g. a bleed occurring with unknown day and month in 2024 when censoring occurred in 2023).

Other than the cases described above, imputation will not be performed for any other missing data, unless specified otherwise.

5.7. Censoring Rules

The duration of efficacy follow-up time for the calculation of annualized rates (bleeding or infusion rates) and efficacy analyses relating to FVIII:C activity levels will be censored when a participant has a complete loss of FVIII activity and/or is returned to prophylaxis in the investigator's clinical judgement. Complete loss of FVIII activity is defined as when the central or local lab one-stage FVIII activity level falls to less than or equal the diagnostic historical value 28 days or later following SPK-8011 infusion. Return to prophylaxis will be considered when the participant returns to FVIII prophylaxis or non-FVIII prophylaxis therapy post SPK-8011 infusion. Censoring will start at the earliest date of either complete loss of FVIII activity or return to prophylaxis. Bleeding events that occur after censoring will not be included in ABR or AIR calculations. All efficacy assessments that occur after the censoring date will not be summarized, unless specified otherwise.

5.8. Visits and Visit Windows

The planned analyses do not require visit window calculations unless specified otherwise.

For the following assessments: Hemophilia Joint Health Score, Hemophilia Activities List Questionnaire, Haem-A-QoL questionnaire, and EQ-5D-5L questionnaire, assessments are mapped to post-baseline visits as follows: for each post baseline assessment timepoint of interest, the first assessment that occurred at least that long after dosing is mapped to that visit. For example, for the Week 52 timepoint, an assessment is mapped to Week 52 if it is the earliest assessment that occurs at least 52 weeks after SPK-8011 infusion.

Unscheduled visits will be included in listings and individual plots, unless specified otherwise. Unscheduled visits will not be summarized in tables unless they are included as a part of nominal week/year means of FVIII:C activity level.

Unless otherwise specified, data will be analyzed according to nominal timepoints.

5.8.1. Nominal Weeks

Nominal week of follow-up is defined as the ceiling value of the difference in days between the lab visit date and the SPK-8011 infusion date divided by 7. For example, nominal week 4 will be assigned to days 22 through 28 of follow-up.

5.8.2. Gaps in follow-up

Due to the structure of the Phase 1/2 clinical program with a separate, dedicated LTFU study, administrative gaps (herein denoted as gaps) in follow up time occurred in a few participants who completed SPK-8011-101 and had a delay in enrollment into the LTFU study. Additionally, during the amendment of the LTFU study from a 4-year study to a 9-year study, additional administrative gaps impacted the follow up of a few participants who had

completed the 4-year LTFU and had a delay in re-enrollment into the 9-year LTFU, also resulting in gaps. Efficacy and safety follow up times are restricted to the time where participants are under consent; thus, these two types of gaps in follow up are removed from the efficacy and safety follow-up time calculations. The two types of gaps will be denoted as: i) Gap A (i.e. between the SPK-8011-101 study and LTFU enrollment), and ii) Gap B (i.e. during LTFU), and will be derived as follows:

- Gap Day A = Number of Gap A days = max{0,(Informed Consent Date of LTFU – End of Study Date SPK-8011-101) – 1}
- Gap Day B = Number of Gap B days = max{0,(Informed Consent Date of Protocol Amendment 2 – "Month 48" visit date) – 1}

Safety follow-up time in days (SAF FUP) will be calculated as:

- SAF FUP = lesser of (date of study withdrawal or date of last contact (across study SPK-8011-101 and LTFU)) - SPK-8011 infusion date + 1 – Gap Day A – Gap Day B

Efficacy follow-up time in days (EFF FUP) will be calculated as:

- EFF FUP = lesser of (date of study withdrawal, date of last contact or date of censoring) - SPK-8011 infusion date – 28 + 1 – I(censoring occurred after Gap A)*Gap Day A – I(censoring occurred after Gap B)*Gap Day B

Where the indicator function I(.) = 1 if the condition in the brackets is met, 0 otherwise.

6. STUDY PATIENTS

6.1. Participant Disposition

Participant disposition data and screen failure reasons will be listed.

The following participant disposition data will be summarized by SPK-8011 dose group and overall.

The number of participants in the FAS, who completed, are ongoing, and discontinued, from the SPK-8011-101 study along with the reason for study discontinuation, where applicable. Additionally, the number of participants who entered the LTFU study, are ongoing in the LTFU study, completed LTFU, and reasons for discontinuation, where applicable, will also be summarized.

Safety and efficacy follow-up time (i.e. SAF FUP and EFF FUP respectively), and the chronological time since SPK-8011 infusion (i.e. the difference between the SPK-8011 infusion date and the date of last contact) in weeks will be calculated for each participant and summarized descriptively by SPK-8011 dose group, and overall.

6.2. Protocol Deviations

Major and minor protocol deviations will be listed by participant.

6.3. Demographic and Baseline Characteristics

The following participant baseline characteristics will be summarized overall and by SPK-8011 dose group and listed:

- Demographics: Age at informed consent, sex, race, ethnicity, BMI (kg/m2), BMI group (<= 30, >30), prior FVIII Use (on-demand, prophylaxis)
- Hemophilia History: Age at diagnosis, HCV antibody result, HIV antibody result, FVIII severity level (FVIII <1%, 1-2% [inclusive]), History of FVIII Inhibitors, number of spontaneous bleeds (and joint spontaneous bleeds) in past 52 weeks at Screening by prior FVIII use, number of traumatic bleeds (and joint traumatic bleeds) in past 52 weeks by prior FVIII use, FVIII inhibitor Bethesda titer

Additional baseline characteristics (e.g. hepatitis B results) may be included in summary outputs.

6.4. Medical History and Current Medical Conditions

Coded terms of medical and surgical history will be listed by participant and may be summarized descriptively.

6.5. Prior Medications and Procedures

Prior medication data including ATC pharmacologic class (ATC level 2 and coded using the WHO Drug Dictionary, Mar2021) and product name preferred term will be listed by participant. Prior medications are those which have a start date and stop date prior to the SPK-8011 infusion date. Prior procedures will also be listed by participant.

6.6. Concomitant Medications and Procedures

The incidence and frequency of use of concomitant medications, immunomodulatory drugs, and procedures will be listed and summarized by ATC pharmacologic class (ATC level 2 and coded using the WHO Drug Dictionary, Mar2021), SPK-8011 dose group. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving 30 days prior to screening, at the time of enrollment or receives during the study must be recorded in the eCRF along with reason for use, start and end dates, and dosage information including dose and frequency. "Concomitant" is defined as any intervention with a start date on or after the date of SPK-8011 administration, or any medication which started prior to SPK-8011 dosing and continued after dosing. Imputation for partial or missing start dates will be handled as per

Section 3.7 of this SAP; the imputed date will then be used to determine if the concomitant definition has been met.

A separate summary of time to corticosteroids (CS) will include:

- Days from SPK-8011 infusion to first oral CS dose
- Duration of oral CS dose
- Days from SPK-8011 infusion to first IV CS dose
- Duration of IV CS dose
- Duration of either oral or IV CS dose amongst subjects who received IV methylprednisolone (IVMP)
- Duration of either oral or IV CS dose amongst subjects who received oral CS

Duration of immunomodulatory therapies will be listed.

7. EXPOSURE ANALYSIS

SPK-8011 dosing information for each participant will be listed.

8. EFFICACY ANALYSIS

8.1. Annualized Bleeding Rate

The number of bleeding events will be analyzed using the annualized bleeding rate (ABR) per participant beginning 28 days following SPK-8011 administration. The following bleed types will be considered:

Table 1: Bleed Types

Bleed Type	Description
All Bleeds/Total 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.
Spontaneous Bleeds	A bleed is considered to be a "spontaneous bleed" if it is reported on the eCRF as being spontaneous.
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.

The International Society on Thrombosis and Haemostasis (ISTH) 72-Hour Rule will be implemented for derivation of ABR for "all bleeds" categories:

- A bleeding episode starts from the first sign of a bleed and ends no more than 72 hours after the last injection to treat the bleed or the last untreated bleed at the same location, within which any sign of bleeding at the same location or injections ≤ 72 hours are considered the same bleeding episode.
- Any injection or untreated bleed occurring more than 72 hours after the preceding one will be considered the start of a new bleeding episode. Any subsequent injection or untreated bleed at a different location will be considered a separate bleeding episode, regardless of the time from the last injection or bleed.

The following calculated ABR will be summarized descriptively (rounded to the hundredth decimal place):

i) ABR for bleeds observed/recorded 28 days post SPK-8011 administration will be computed as:

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

Where EFF FUP, the duration of efficacy follow-up, is defined in Section 5.8.2.

Summary tables describing ABR will be presented by SPK-8011 dose group and overall for:

- All subjects
- Subjects entering the study using prophylaxis FVIII

- Subjects entering the study using on-demand FVIII

Separate summary tables will describe the prior to SPK-8011 administration retrospectively documented bleeds over 52 weeks for participants on prior prophylaxis, and on prior on-demand therapy.

The number and proportion of participants with a 28 days post SPK-8011 administration ABR of 0, >0 to <=1, >1 to <=2 or >2 will be summarized.

A regression model-based mean ABR and ABR ratio comparing a participant's ABR to the hemophilia historically documented ABR for the 52-weeks prior to SPK-8011 administration with the associated 95% confidence intervals (CIs) will be estimated from a mixed-effects negative binomial regression model with a log-link. The model will include time period as a categorical fixed effect (i.e. 52 weeks prior to SPK-8011 infusion vs. 28 days post SPK-8011 infusion), and participant as a random effect. In addition, separate models will be created for subjects with prior prophylaxis and for prior on-demand therapy. These analyses will only be produced for all bleeds and spontaneous bleeds. Model fit will be examined to evaluate convergence issues.

All ABR parameters will be listed by participant.

8.2. Annualized FVIII Infusion Rate

The number of recorded FVIII infusion events resulting from a bleeding episode using the "All bleeds" definition in Table 1 will be analyzed using the annualized infusion rate (AIR) per participant beginning 28 days following SPK-8011 administration (rounded to the hundredth decimal place respectively):

i) AIR will be calculated as follows:

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

Where EFF FUP, the duration of efficacy follow-up, is defined in Section 5.8.2.

Summary tables describing AIR will be presented by SPK-8011 dose group and overall for:

- All subjects
- Subjects entering the study using prophylaxis FVIII
- Subjects entering the study using on-demand FVIII

8.2.1. Linking Infusions and Bleeds

FVIII infusions linked to bilateral bleeds in the FVIII infusion log will be programmatically linked to both left and right bleeds due to database limitations. Similarly, the FVIII infusion

log will be linked in case a participant is treated with a single infusion for two bleeds in different locations (e.g. an ankle bleed and a knee bleed at the same time).

8.3. FVIII:C Activity

For all FVIII:C assessments, summaries and supportive listings will be generated and the following exclusion rules related to FVIII:C assessments will be applied:

1. If a FVIII:C assessment occurs within 5 days after a FVIII infusion (including FVIII infusions prior to SPK-8011 administration) or within 135 days following administration of emicizumab (Hemlibra), then that assessment will be excluded from all calculations and summaries.

2. FVIII:C assessments occurring after censoring will be excluded from all calculations and summaries.

Mean FVIII:C activity levels (one stage and chromogenic separately; central lab-recorded) may be summarized at nominal weeks 2, 4, 6, 8, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44, 48 and 52 from SPK-8011-101 administration, and every 12 weeks afterwards.

To summarize FVIII:C activity level by nominal week, the median will be computed for each participant using all recorded data collected up to and including the nominal week of interest, since the prior nominal week of interest. For example, nominal week 28 activity level for each participant will be the median for all values obtained across nominal weeks 25, 26, 27 and 28. Median FVIII activity levels will also be summarized by nominal week using OSA and CSA central laboratory results.

Peak FVIII:C activity (OSA and CSA; central lab-recorded), as well as time to peak FVIII:C activity, will be summarized by SPK-8011 dose group and overall, and will be listed by participant. The above exclusion rules will apply to peak FVIII:C activity summaries.

Separate listings of participants with a complete loss of FVIII expression (as defined in Section 5.7), FVIII:C activity levels occurring prior to censoring (as defined in Section 5.7), and of participants with FVIII:C activity levels > 200% (i.e. supraphysiologic FVIII) may be provided.

Analysis of specified FVIII thresholds will be conducted at nominal weeks 28, 32, 36, 40, 44, 48, and 52 from SPK-8011-101, and 64, 72, 84, 96, etc. from LTFU. For each participant, the median OSA, central lab recorded FVIII:C activity level will be computed for each nominal week, using all data collected up to and including the nominal week of interest since the prior nominal week of interest. The proportion of participants who maintain a median FVIII:C activity level ≥ 5% across the nominal weeks above will be estimated. As a sensitivity analysis, the proportion of participants with a maintained median FVIII:C activity level ≥ 12% will also be analyzed.

The following graphical displays of FVIII:C activity levels (one-stage; central lab-recorded) will be generated:

- Individual OSA FVIII:C activity level (i.e. a spaghetti plot). This plot will display all raw FVIII:C values, except for those assessments excluded by exclusion rules 1-2 above.
- FVIII:C activity level as measured by central OSA will be summarized graphically using a box plot. The following windowing will apply to FVIII:C assessments: nominal weeks 0-2, >2-6, >6-10, >10-14, >14-18, >18-22, >22-26, >26-30, >30-34, >34-38, >38-42, >42-46, >46-50, >50-54, etc. The median FVIII value for each individual subject within each time interval will be derived.
- A scatterplot of all OSA vs. CSA (central lab-recorded, except for those assessments excluded by the above exclusion rules) FVIII activity values following SPK-8011 administration. The plot will include a fitted regression line characterizing this relationship, slope with 95% CI, and Pearson correlation coefficient. A second version of this plot will also be generated, showing both the Y-axis and X-axis on a log scale.

8.3.1. FVIII and Annualized Bleeding Rate Correlation Analysis

The relationship between the spontaneous bleeds ABR and average FVIII:C activity (OSA central-lab recorded; weighted by duration of FVIII:C activity and excluding assessments during the initial 28 days post SPK-8011 infusion) will be analyzed using a negative binomial regression model. For this analysis, the average FVIII:C activity will be computed by estimating the area under the FVIII:C activity curve and dividing by the difference of the study day of the last FVIII:C assessment and the study day of the first FVIII:C assessment. The trapezoidal rule will be used to approximate the area under the FVIII:C activity curve. To implement this, for each consecutive pair of FVIII:C assessments occurring on Day_i and Day_{i+1}, the following will be calculated: $(Day_{i+1} - Day_i)*(FVIII:C_i + FVIII:C_{i+1})/2$. This is repeated for each consecutive pair of FVIII:C assessments for each participant and cumulatively added together.

For the negative binomial regression model, the dependent variable is the number of treated bleeds from 28 days post SPK-8011 infusion throughout follow-up or censoring (if applicable). The independent variable, x_i is the average FVIII:C activity from 28 days post infusion, and the offset variable t_i represents the duration of efficacy follow-up (i.e. EFF FUP). The regression model represents the mean function of the dependent variable $\mu_i = \frac{t_i}{365.25} \exp(\beta_0 + \beta_1 x_i)$ where μ_i can be interpreted as the expected ABR given an average FVIII:C activity level. A scatterplot of the average FVIII activity vs. the spontaneous bleeds ABR with the corresponding estimated regression curve from the above regression model will be generated. A separate scatterplot will also be generated comparing average FVIII

activity vs the spontaneous bleeds ABR. A separate version of this analysis will be done using CSA central-lab FVIII:C activity levels, but as otherwise described above.

9. EXPLORATORY ENDPOINTS

All analyses described in this section will be censored according to the censoring rule regarding the loss of FVIII expression or return to prophylaxis therapy, such as FVIII prophylaxis or Hemlibra described in Section 5.7. That is, assessments that occurred after the loss of FVIII expression or the start of the return of prophylactic treatment will not be included in summaries.

9.1. Joint Assessments

9.1.1. Target Joints

The definition of a target joint is any single joint into which three or more spontaneous bleeds occur within a consecutive 6-month period. Where there have been ≤ 2 spontaneous bleeds into the joint within a consecutive 12-month period, the joint is no longer considered a target joint. Baseline target joints are assessed at Day 0 by the investigator for participants enrolled after protocol amendment 7; for participants enrolled prior to protocol amendment 7, the baseline target joint data were retroactively entered by the investigator. Resolution of target joints following SPK-8011 administration is derived based on the bleeds recorded in the bleeding event log. The time point at which a target joint is said to be resolved is the earliest day in which there is a minimum of 12 months since SPK-8011 administration and there have been ≤ 2 spontaneous bleeds into the joint within a consecutive 12-month period. Target joints at baseline and resolution of target joints will be listed and summarized descriptively.

9.1.2. Hemophilia Joint Health Score (HJHS)

The current Hemophilia Joint Health Score (HJHS) comprises an assessment of specific features, or items, of the six index joints and an assessment of global gait. For each of the six joints, the following items are scored: swelling (scored 0-3), duration of swelling (0-1), muscle atrophy (0-2), crepitus on motion (0-2), flexion loss (0-3), extension loss (0-3), joint pain (0-2), strength (0-4) and gait is scored 0 to 4. Scores from the individual items are added together to give a joint score; joint scores and the global gait score are added together to give a total score. Higher scores indicate greater joint damage.

The proportion of participants in each response category for swelling, muscle atrophy, crepitus on motion, flexion loss, extension loss (from hyperextension), strength and global gait will be presented using the designated response definitions for each assessment type. The proportion of participants falling into each response category will be tabulated by visit (baseline, week 26, 52/EOS, 78, 104, 130 156, etc.), and SPK-8011 dose group, and overall.

HJHS assessments with non-evaluable (NE) components are excluded from summary analysis.

Summary statistics will be presented for the global gait score and HJHS total score and listed. Summary statistics will also be generated for the change from baseline for the gait score and HJHS total score at each follow-up time point. Any HJHS assessment with non-evaluable components will be excluded from all summaries.

9.2. Activity Assessments

9.2.1. Hemophilia Activities List Questionnaire

The scoring and normalization algorithms described below will be used to obtain normalized scores (range: 0-100) where 0 represents the worst possible functional status for the domain of interest and 100 represents the best possible function status for that domain. The algorithms provide a mechanism for handling missing data within the normalizing procedure.

Prior to normalizing, recoding is required for scoring each item. Recoding will occur using the following table:

Table 1. Hemophilia Activities List Recoding

Score	Recode	Meaning
8	0	N/A
1	6	Impossible
2	5	Always a problem
3	4	Mostly a problem
4	3	Sometimes a problem
5	2	Rarely a problem
6	1	Never a problem

After recoding, raw domain and summary scores will be calculated accordingly:

Table 2. Raw Domain and Summary Scoring Using Recoded Item Scores

Domain or Summary Score	Items
Lying/Sitting/Kneeling/Standing (LSKS)	1-8 (8)
Functions of the Legs (LEGS)	9-17 (9)
Functions of the Arms (ARMS)	18-21 (4)
Use of Transportation (TRANS)	22-24 (3)
Self Care (SELFC)	25-29 (5)
Household Tasks (HOUSEH)	30-35 (6)
Leisure Activities and Sports (LEISPO)	36-42 (7)
Upper Extremity Activities (UPPER)	18-21, 25-29 (9)
Basic Lower Extremity Activities (LOWBAS)	8-13 (6)
Complex Lower Extremity Activities (LOWCOM)	3, 4, 6, 7 ,14-17, 22 (9)
Sum Score (SUM)	1-42 (42)

Domain and summary scores will then be normalized using the following formulas:

Table 3. Normalization of Domain and Summary Scores

Domain or Summary Score	Normalization Formula
Lying/Sitting/Kneeling/Standing (LSKS)	100-[($\sum_{1-8}$ – valid)*(100/(5*valid))]
Functions of the Legs (LEGS)	100-[($\sum_{9-17}$ – valid)*(100/(5*valid))]
Functions of the Arms (ARMS)	100-[($\sum_{18-21}$ – valid)*(100/(5*valid))]
Use of Transportation (TRANS)	100-[($\sum_{22-24}$ – valid)*(100/(5*valid))]
Self Care (SELFC)	100-[($\sum_{25-29}$ – valid)*(100/(5*valid))]
Household Tasks (HOUSEH)	100-[($\sum_{30-35}$ – valid)*(100/(5*valid))]
Leisure Activities and Sports (LEISPO)	100-[($\sum_{36-42}$ – valid)*(100/(5*valid))]
Upper Extremity Activities (UPPER)	100-[($\sum_{18-21;25-29}$ – valid)*(100/(5*valid))]
Basic Lower Extremity Activities (LOWBAS)	100-[($\sum_{8-13}$ – valid)*(100/(5*valid))]
Complex Lower Extremity Activities (LOWCOM)	100-[($\sum_{3-4;6-7;14-17;22}$ – valid)*(100/(5*valid))]
Sum Score (SUM)	100-[($\sum_{1-42}$ – valid)*(100/(5*valid))]

where valid = number of items scored within a specific domain/component. Items with "n/a" response are to be considered NOT valid.

Summary statistics will be obtained for each domain/component and for the total summary score at baseline (pre-dosing) and at weeks 7, 12, 14, 26, 40, 52/EOS, 78, 104, 130 156, etc. of follow-up by SPK-8011 dose group and overall. Summary statistics will also be generated for the change from baseline to each follow-up time point. Summary statistics will not be provided for individual item scores, as the algorithm specifically details the computation of domains as the basic "raw data" unit for evaluation; individual item score results will be included in a data listing. Depending on the number of participants who discontinue from the study prior to week 52, an additional summary of participants who complete the study will be considered prior to locking the database.

Data collected on the use of adaptations or aids to perform certain activities will be provided in a listing.

9.3. Quality of Life Assessments

9.3.1. Haem-A-QoL

For the Haem-A-QoL questionnaire, 10 domains are derived among the 46 individual questionnaire items and are fully elucidated in Appendix 3 of the study protocol. The domains are:

Physical health in the past 4 weeks (5 questions)
How have you been feeling about your hemophilia in the past 4 weeks? (4 questions)
How does hemophilia affect your view of yourself in the past 4 weeks (5 questions)
Sports and leisure in the past 4 weeks (5 questions)
Work and school in the past 4 weeks (4 questions)

Dealing with hemophilia in the past 4 weeks (3 questions)
Treatment in the past 4 weeks (8 questions)
Future recently (5 questions)
Family planning recently (4 questions)
Partnership and sexuality recently (3 questions).

For each question within each domain, available responses (numeric coding) are given as: Never (1), Rarely (2), Sometimes (3), Often (4), and All the Time (5), with additional possible responses of Ineligible (6), Missing (7), or Not Applicable (8). The data listing will display the actual recorded response from the electronic case report form. However, for any data analysis, question responses scored greater than a 5 will be set to a missing value. In addition, while 36 questions are worded in a "negative tending" manner, 10 questions worded in a positive manner will have their scoring reversed using the formula: 6 minus the question score, to properly account for directionality. These are:

Domain #3, question 2: I felt comfortable in my body
Domain #3, question 5: I was able not to think all the time of my hemophilia
Domain #4, question 3: I played sports just as much as others
Domain #5, question 1: I was able to go to work/school regularly in spite of my hemophilia
Domain #5, question 2: I was able to work/study like healthy colleagues
Domain #6, question 1: I tried to recognize early when a bleed developed
Domain #6, question 2: I was able to tell whether or not I was bleeding
Domain #6, question 3: I was able to control my bleeds
Domain #7, question 8: I was satisfied with the hemophilia center
Domain #8, question 2: I have been expecting that things will get better in the future.

For each participant, there are 3 steps in the process of deriving the transformed scale score which is used for all the analysis

1. Raw Scale Score: Derived as the sum of all items in a scale., e.g. the raw score for physical health is the sum of the 5 items from this scale. A total score is calculated by summing up all of the raw and reverse coded items in the available scales.

2. Standardized Scale Score: To get the standardized scale score, the raw scale score is divided by the number of items in the scale. That way a comparison of scores across scales per patient is possible.

3. Transformed Scale Score: The scores for each scale is normalized to a 100-point scale, computed as follows:

$$TSC = 100 \times \frac{raw\ scale\ score - minimal\ possible\ raw\ score}{possible\ range\ of\ raw\ scale\ scores}$$

In general, a domain score can be calculated if ≥ 50% of the Haem-A-QoL items have been answered otherwise it is set to missing even if 1 item have been answered. Patients can answer "Not applicable" in the Haem-A-QoL to questions in the sports and leisure, work and school, and family planning scales. In this case, the minimum number of items that needs to be completed and not responded to as "Not applicable" is:

- Sports and leisure: 3
- Work and school: 2
- Family planning: 2

Lower Haem-A-QoL scores indicate better quality of life.

Summary statistics will be generated for the transformed scale scores for each of the 10 domains and overall. Summary statistics will be obtained at baseline (pre-dosing), week 26, 52/EOS, 78, 104, 130 156, etc. and on the change from baseline to each post-dose assessment by SPK-8011 dose group. Depending on the number of participants who discontinue the study prior to week 52, an additional summary of participants who complete the study will be considered prior to locking the database. Individual questions will not be summarized; they will only be presented in the data listing.

9.3.2. European Quality of Life–5 Dimensions–5 Levels

The European Quality of Life–5 Dimensions–5 Levels (EQ-5D-5L) is a standardized measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of 2 components: a descriptive system of the respondent's health and a rating of his or her current health state using a 0 to 100 mm VAS. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his or her health state by ticking (or placing a cross) in the box associated with the most appropriate statement in each of the 5 dimensions. The VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labeled "best imaginable health state" and "worst imaginable health state." This information can be used as a quantitative measure of health outcome.

Scores from the descriptive component can be reported as a five-digit number ranging from 11111 (full health) to 55555 (worst health) and can be converted into a single index values (utilities) using country specific value sets (see 6.2 for sample SAS code in calculating index score). This index values are a major feature of the ED-5D instrument, facilitating the calculation of quality-adjusted life years (QALYs) used to inform economic evaluation of health care interventions

Scores from the continuous component (EQ-VAS) are numbers between 0 and 100 (0 representing the worst health and 100 the best health) on the EQ VAS scale. The number marked on the scale will be the value used for analysis.

Overall health state using US weighting algorithm at each assessment time point will be summarized along with change from baseline using descriptive statistics.

For the EQ-5D-5L questionnaire, both continuous-based (VAS) and index score and the categorical scales (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) will be summarized for each of the 5 categories by SPK-8011 dose group and overall. Additionally, the overall EQ-5D health state at each visit will be determined based on the response to each category as follows:

- Improved health: improvement from baseline observed on at least one category, and no worse in any other category.
- Worse health: worse relative to baseline in at least one category, and is no better in any other category
- No health change: no improvement or worsening in any category relative to baseline
- Mixed health change: improvement in at least one category and worsening in at least one category relative to baseline

Summary statistics will be presented at nominal weeks 26, 52/EOS, 78, 104, 130 156, etc. Results will also be listed.

9.3.3. Health Economic Assessments

Health economic parameters will be listed for baseline and at nominal weeks 7, 12, 14, 26, 40, 52/EOS, 78, 104, 130 156, etc. The parameters collected are:

- Number of hospitalizations (excluding pre-planned hospitalizations documented at screening)
- Number of hospitalization days
- Number of emergency room visits
- Number of physician visits, excluding study visits
- Number of days off from school or work.

The assessment at baseline will encompass the prior 52 weeks prior to SPK-8011 infusion. Hence, data collected at each post-baseline visit will be summed by year to provide a post SPK-8011 infusion total for each post SPK-8011 infusion year. Additionally, an annualized rate for each parameter will be calculated using the following structure:

Annualized Hospitalization Rate

$$\text{AHR} = \frac{365.25 * total\ number\ of\ post\ SPK-8011\ infusion\ hospitalizations}{date\ of\ last\ health\ economics\ assessment\ minus\ SPK-8011\ infusion\ date}$$

Where the denominator will also exclude Gap A Days and Gap B Days. Similar annualized parameters will be calculated for hospitalization days, emergency room visits, physician visits and days off from school or work.

Each parameter will be summarized by visit, yearly total and annualized rate by SPK-8011 dose group and overall, and listed. Change from baseline will be summarized for the post SPK-8011 infusion yearly total and annualized rate for each parameter.

10. SAFETY

10.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant temporally associated with the use of the study drug, regardless of causal relationship. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) with an onset date on or following SPK-8011 administration. AEs with partial onset dates will be considered treatment-emergent if the imputation described in Section 5.6 of this SAP results in an onset date on or after the date of SPK-8011 infusion.

An overall summary table will present participants with at least one of the following AE categories along with the corresponding event frequencies, and will be produced overall and by SPK-8011 dose group:

- TEAEs (I.e. AEs occurring post SPK-8011 administration)
- TEAEs related to SPK-8011
- Serious TEAEs
- Serious TEAEs related to SPK-8011
- AEs and Serious AEs (SAEs) related to immunomodulation agents
- TEAEs by maximum severity (mild, moderate, severe)
- AEs of special interest (AESIs) (see Section 9.1.3 of the SPK-8011-101 study protocol).

The following summaries of adverse events will be produced overall and by SPK-8011 dose group. Each summary table will be created separately for SPK-8011-101, SPK-8011/8016-LTFU, and both studies combined.

- Incidence and frequency of TEAEs

- Incidence and frequency of serious TEAEs
- Incidence and frequency of TEAEs (and serious TEAEs) recorded as related to SPK-8011
- Incidence and frequency of AEs (and SAEs) recorded as related to Immunomodulation agents
- Incidence of TEAEs by maximum severity.

All summaries will be classified by MedDRA version 23.0 system organ class (SOC) and preferred term. A separate summary table of TEAEs by preferred term only will also be provided. Adverse events will also be listed by subject.

10.2. Clinical Laboratory Data

Clinical laboratory data will be listed and will include the following parameters:

1. Hematology: white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils; red blood cell (RBC) count (hemoglobin, hematocrit, platelet count)
2. Clinical chemistry: sodium, potassium, chloride, bicarbonate, glucose, phosphate, serum creatinine, blood urea nitrogen (BUN). If collected and reported, C-reactive protein (CRP).
3. Liver function tests: albumin, total bilirubin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH)
4. Coagulation: FVIII antigen, FVIII inhibitor, activated partial thromboplastin time (aPTT).
5. FVIII activity data including central OSA, central CSA, and local FVIII activity data (OSA) will be presented in separate listings.

Laboratory tests that are not graded by CTCAE V5.0 criteria will be presented as changes in normal range values (eg. low, normal, high).

Maximum ALT (central lab) will also be summarized graphically using a box plot during the first 52 weeks following SPK-8011 infusion. The following windowing will apply to ALT assessments: nominal weeks 0-2, >2-6, >6-10, >10-14, >14-18, >18-22, >22-26, >26-30, >30-34, >34-38, >38-42, >42-46, >46-50, >50-54, etc. In the event of multiple ALT assessments within a window for a participant, the maximum ALT value for that participant will be summarized in the box plot.

Additionally, ALT kinetics (local lab) will be analyzed. The parameters of interest for ALT kinetics are:

- Time until first ALT increase of at least 1.5 x baseline ALT: (date of initial ALT assessment that meets definition) – (SPK-8011 infusion date)
- ALT value at first ALT increase of at least 1.5 x baseline ALT
- Time until first ALT increase above ULN: (date of initial ALT assessment that meets definition) – (SPK-8011 infusion date)
- ALT value at first ALT increase above ULN
- Time until maximum ALT value in the first 52 weeks: (date of initial ALT assessment that meets definition) – (SPK-8011 infusion date)
- ALT maximum value in the first 52 weeks

These parameters will be listed and summarized by SPK-8011 dose group and overall.

AAV Neutralizing Antibody data will be presented in listings.

10.3. Physical Examination

Physical examinations including abnormal examination findings will be listed by participant.

10.4. Vital Signs

Vital sign parameters will be listed by participant with clinically notable changes from baseline in vital signs included. Specific definitions of the criteria for generation of this listing will be made prior to database lock. These may include specifications of out-of-range clinically meaningful trigger values, stated absolute or percent change from baseline maximums and individual changes noted by the investigator as clinically noteworthy.

11. PHARMACOKINETICS

11.1. Vector-shedding of SPK-8011

Vector-shedding of SPK-8011 in bodily fluids will be presented in a data listing by SPK-8011 dose group for clinical review and will include copies of SPK-8011 per microgram of DNA tested (PBMC) and copies of SPK-8011 per mL of sample tested (saliva, semen, serum, urine). In addition, time to below quantifiable limits (BQL; non-detectable SPK-8011 vector) in days will be calculated for each bodily fluid for each participant and summarized descriptively by SPK-8011 dose group and overall. Subjects with missing results prior to their first BQL are excluded from analysis (each specimen handled separately). Time to BQL will be calculated for each bodily fluid for each participant as follows: nominal week of the first assessment with a result of BQL – SPK-8011 infusion date + 1.

Additionally, a plot of percentage of participants with detectable vector shedding post SPK-8011 infusion by week will be generated with all specimen types plotted together.

12. INTERIM ANALYSIS

As this is an open-label, non-randomized study, data retrieval and generation of ongoing data listings for internal review are undertaken in a dynamic, *ad hoc* manner. Therefore, there is no formal interim analysis and no statistical testing. Regulatory considerations, Sponsor publications and/or DMC may require interim generation of output on an as-needed basis, with appropriate specification of data cutoff dates for any required submissions prior to completion of the study. This implies that such output could be generated while the SAP is still considered a draft, even a final draft. However, no final analysis of the data will be undertaken prior to final database lock of the LTFU study.

13. CHANGES FROM PROTOCOL SPECIFIED ANALYSIS

The following endpoints will not be analyzed as per Protocol SPK-8011-101:

- Incidence of clinically significant abnormal laboratory values
- Time to achieve steady-state FVIII activity level
- Steady-state FVIII activity levels
- Incidence of immune responses to AAV capsid protein and B-domain-deleted human FVIII (BDD-hFVIII) transgene
- Safety endpoint hepatic transaminase elevation requiring immunosuppression

14. LIST OF TABLES, LISTINGS, AND FIGURES

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

15. APPENDIX

15.1. Example SAS Code

Example SAS Code for Negative Binomial Regression

```
PROC GENMOD DATA=dat;
where paramcd='TOTBLEED';
CLASS usubjid timeperiod (REF='Prior');
MODEL aval= timeperiod / DIST=negbin LINK=log OFFSET=logfup TYPE3;
REPEATED SUBJECT=usubjid / TYPE=un CORRW;
LSMEANS timepoint / exp cl diff;
ESTIMATE 'AFTER SPK vs. PRIOR' TIMEPOINT 1 -1 / exp;
ESTIMATE 'AFTER SPK ABR' INTERCEPT 1 TIMEPOINT 1 0 / exp;
ESTIMATE 'PRIOR SPK ABR' INTERCEPT 1 TIMEPOINT 0 1 / exp;
RUN;
```

15.2. Example SAS Code

Computing EQ-5D-5L index values with SAS using the United States (US) Pickard value set Version 1.2 (Updated 31/01/2022)

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'.

If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions

in the EQ-5D health profile (i.e. 1, 2, 3, 4 or 5). The variable 'EQindex' contains the values of the EQ-5D-5L index values on the basis of the US set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
**********************************************************************
*SAS syntax code for the computation of index*
*values with the US TTO value set*
**********************************************************************

data WORK.CAT;
```

```
set WORK.CAT;
if mobility eq 1 then disut_mo=0;
else if mobility eq 2 then disut_mo=0.096;
else if mobility eq 3 then disut_mo=0.122;
else if mobility eq 4 then disut_mo=0.237;
else if mobility eq 5 then disut_mo=0.322;
if selfcare eq 1 then disut_sc=0;
else if selfcare eq 2 then disut_sc=0.089;
else if selfcare eq 3 then disut_sc=0.107;
else if selfcare eq 4 then disut_sc=0.220;
else if selfcare eq 5 then disut_sc=0.261;
if activity eq 1 then disut_ua=0;
else if activity eq 2 then disut_ua=0.068;
else if activity eq 3 then disut_ua=0.101;
else if activity eq 4 then disut_ua=0.255;
else if activity eq 5 then disut_ua=0.255;
if pain  eq 1 then disut_pd=0;
else if pain  eq 2 then disut_pd=0.060;
else if pain  eq 3 then disut_pd=0.098;
else if pain  eq 4 then disut_pd=0.318;
else if pain  eq 5 then disut_pd=0.414;
if anxiety eq 1 then disut_ad=0;
else if anxiety eq 2 then disut_ad=0.057;
else if anxiety eq 3 then disut_ad=0.123;
else if anxiety eq 4 then disut_ad=0.299;
else if anxiety eq 5 then disut_ad=0.321;
disut_total=disut_mo+disut_sc+disut_ua+disut_pd+disut_ad;
EQindex=1-disut_total;
Run
```