Official Title: A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Subjects with Severe Haemophilia A

NCT Number: NCT02576795

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 15 May 2019

BIOMARIN®

STATISTICAL ANALYSIS PLAN

Protocol Number: 270-201

Study Title: A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Subjects with Severe Haemophilia A

Sponsor: BioMarin Pharmaceutical Inc.
105 Digital Drive
Novato, CA 94949

Version: 3.0

Date: 15 May 2019

Approvals

Statistical Analysis Plan

Title: A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Subjects with Severe Haemophilia A

Protocol: 270-201, Amendment 8, 31 January 2019

Date: 15 May 2019

Approvals

PI
___/___/___
DD MM YY
0FB511EF91824C8CBBA676C6DA93FCFC

DocuSigned by:
PI
___/___/___
DD MM YY
D81F76E32EA74F83864C63F8E75F1EBE

DocuSigned by:
PI
___/___/___
DD MM YY
Statistical Programmer
CAD6F079BBD54B4EACD0BBBC1BBE3F2E

DocuSigned by:
PI
___/___/___
DD MM YY
477D7E1FE0CB42B7B62C441E35309D64

DocuSigned by:
PI
___/___/___
DD MM YY
027DA7AC705E447B9682C8910CF2CB1D

DocuSigned by:
PI
___/___/___
DD MM YY
Pharmacovigilance
A4D20DB804134F22A24F37345E0019A4

TABLE OF CONTENTS

1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adenovirus-associated virus
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (v4.03)
CTL	Cytotoxic T lymphocytes
DRB	Data Review Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FXa	Coagulation factor Xa
GCP	Good Clinical Practice

GGT	Gamma-glutamyl transferase
HA	Haemophilia A
hFVIII	Human coagulation factor VIII
HLA	High Level Term
ICH	International Conference on Harmonisation
IP	Investigational product
IV	Intravenous
LDH	Lactate dehydrogenase
LT	Liver test
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PRO	Patient reported outcome
PT	Preferred term
Qol	Quality of life
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error

SFU	Spot-forming units
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
TLGs	Tables, listings, and graphs
vg	Vector genomes
WHO	World Health Organization

2.0 INTRODUCTION

This document describes the statistical methods to be implemented in the analysis of data collected under clinical study protocol 270-201, "A Phase 1/2, Dose-Escalation Safety, Tolerability and Efficacy Study of BMN 270, an Adenovirus-Associated Virus Vector-Mediated Gene Transfer of Human Factor VIII in Patients with Severe Haemophilia A" (Amendment 8, 31 January 2019). The SAP contains definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety.

2.1 Study Overview and Objectives

BMN 270 is an AAV5-based gene therapy vector that expresses the SQ form of hFVIII under the control of a liver-selective promoter. BMN 270 will be delivered by single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue. The clinical study 270-201 is a first-in-human study designed to assess the relationship of vector dose to the augmentation of residual FVIII activity and whether these levels are sufficient to alter the clinical phenotype. The relationship of dose to safety will be correlated to the activity of hFVIII in subjects with severe HA.

The primary objectives of the study are:

- To assess the safety of a single intravenous administration of a recombinant AAV5 encoding human coagulation FVIII (AAV5-hFVIII-SQ) vector.
- To determine the dose of AAV5-hFVIII-SQ required to achieve FVIII at or above 5% of normal activity ($\geq$5 IU/dL) at 16 weeks after infusion. The kinetics, duration, and magnitude of AAV-mediated FVIII activity in individuals with haemophilia A will be determined and correlated to an appropriate BMN 270 dose.

The secondary objectives of the study are:

- To describe the immune response to the FVIII transgene product and AAV capsid proteins following systemic administration of AAV5-hFVIII-SQ.
- To assess the impact of BMN 270 on the frequency of FVIII replacement therapy during the study.
- To assess the impact of BMN 270 on the number of bleeding episodes requiring treatment during the study.

2.2 Study Design

This is a first-in-man, phase 1/2 open-label, dose escalation study in subjects with severe haemophilia A. Eligible subjects will enter the dose escalation part of the study, followed by a 16-week Post-Infusion Follow-Up period during which safety and efficacy assessments will be taken. After the primary endpoint analysis at 16 weeks, safety and efficacy will then be assessed for approximately 5 years.

Subjects who provide written informed consent, meet the entry criteria definition of severe HA, and do not have transduction inhibition activity to AAV5 will be eligible to enroll in the study. Participants will be enrolled into one of up to four cohorts according to dose level as a single intravenous (IV) infusion:

Cohort 1: 6E12 vector genomes [vg] per kilogram of body weight
Cohort 2: 2E13 vg per kilogram

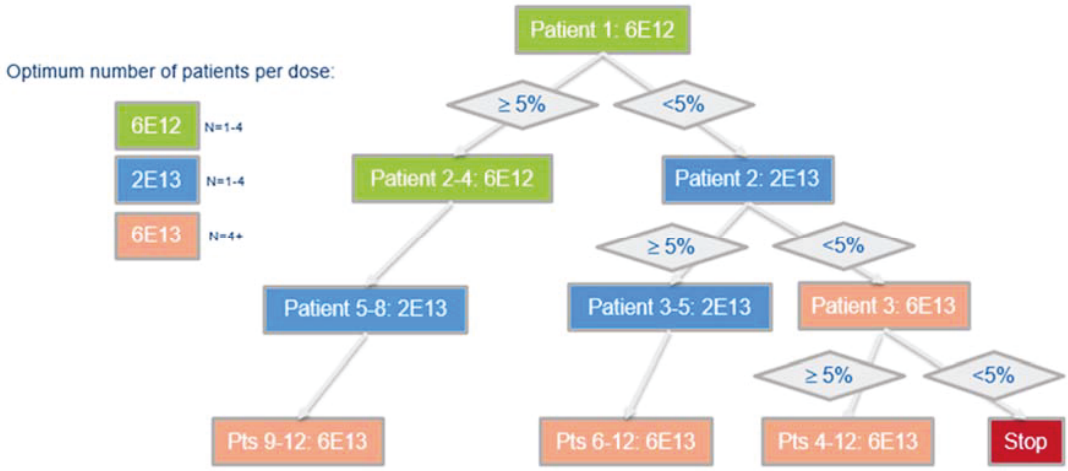
Cohort 3: 6E13 vg per kilogram
Cohort 4: 4E13 vg per kilogram

The starting dose was based on the expression and safety of FVIII observed in nonclinical studies of mice and monkeys. The starting dose has a significant safety margin (10-fold) from no observed adverse effect level (NOAEL) in mice.

Cohort 1-3

The first 3 cohorts will be enrolled sequentially, allowing a period of 3 weeks or more between cohorts. Dose escalation may occur after a single subject in a cohort has been safely dosed if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL in both the one-stage clotting and chromogenic substrate assays. If the FVIII activity reaches ≥ 5 IU/dL at the Week 3 visit and no safety issue is found, then the remaining subjects in the cohort will be enrolled without the need to wait for 3 weeks between subjects. The flow chart of dose escalation scheme for Cohorts 1 to 3 is shown in Figure 2.2.1. Three weeks is expected to be the time the expression will be close to the maximum. This escalation paradigm is intended to minimize the subject numbers exposed to subtherapeutic doses. The decision to escalate to the next dose level will be made based on the review of safety parameters and FVIII activity by the Sponsor and a panel of investigators participating in the study.

Figure 2.2.1: Flow Chart of Dose Escalation Scheme for Cohorts 1 to 3



Cohort 4

For Cohort 4, 3 subjects will be enrolled at 4E13 vg/kg. If FVIII activity in these 3 subjects is ≥ 5% at 8 weeks and if no safety issue is found, an additional 3 subjects may be enrolled in this cohort.

All Cohorts

There will be an ongoing review of individual subject safety and efficacy data by the medical monitor and

the DRB. The adaptive nature of this trial allows the DRB to recommend allocating subjects to the cohorts based on activity levels of FVIII and safety signals.

Because subjects develop neutralizing immunity upon exposure to the AAV5 capsid, re-challenge of vector is not a likely treatment option, and these subjects have effectively a single opportunity for therapy using this AAV capsid. Efficacy will be determined by FVIII activity at 16 weeks post-dose. Safety will be evaluated for approximately 5 years after dosing. Any safety signal may trigger a review of the data and possible additional immunogenicity studies that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMC). Additionally, if any of the events listed in protocol Section 9.3.4.1 occur, enrollment into the trial will be halted to complete an extensive safety analysis. Notification of the study enrollment halt will be sent by the Sponsor to the participating sites via telephone and email immediately after becoming aware of a safety concern. This will ensure no additional subjects are dosed until the signal has been completely evaluated. If, following safety review by the DRB and the Sponsor, it is deemed appropriate to restart dosing, a request to restart dosing with pertinent data will be submitted to the health authority.

2.3 Study Population

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

- Males that are 18 years or older with established severe haemophilia A as evidenced by their medical history. Subjects will be considered as severe if their base FVIII level is 1 IU/dL or less
- Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs)
- Greater or equal to 12 bleeding episodes only if on on-demand therapy over the previous 12 months. Does not apply to subjects on prophylaxis
- Able to sign informed consent and comply with requirements of the trial
- No history of inhibitor, and results from a modified Nijmegen Bethesda assay of less than 0.6 Bethesda Units (BU) on 2 consecutive occasions at least one week apart within the past 12 months
- Sexually active subjects must be willing to use an acceptable method of contraception such as double barrier, including hormonal contraception for at least 6 months post treatment. After 6 months, subjects may stop contraception use only if they have had 3 consecutive negative semen samples.

Subjects are not eligible for this study if they meet any of the following exclusion criteria:

- Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- Any evidence of active infection or any immunosuppressive disorder.
- HIV positive

- Significant liver dysfunction as defined by abnormal elevation of:
    - ALT (alanine transaminase) to 3 times the upper limit of normal;
    - Bilirubin above 3 times the upper limit of normal;
    - Alkaline phosphatase above 3 times the upper limit of normal; or
    - INR (international normalized ratio) ≥ 1.4
- Potential participants who have had a liver biopsy in the past 3 years are excluded if they had significant fibrosis of 3 or 4 as rated on a scale of 0-4
- Evidence of any bleeding disorder not related to Haemophilia A
- Platelet count of < 100 x 10^9/L
- Creatinine ≥ 1.5 mg/dL
- Liver cirrhosis of any etiology as assessed by liver ultrasound
- Hepatitis B if surface antigen is positive
- Hepatitis C if RNA is positive
- Treatment with any IP within 30 days prior to the end of the screening period
- Any disease or condition at the physician's discretion that would prevent the patient from fully complying with the requirements of the study including possible corticosteroid treatment outlined in the protocol. The physician may exclude subjects unwilling or unable to agree on not using alcohol for the 16-week period following the viral infusion.
- Prior treatment with any vector or gene transfer agent
- Major surgery planned in the 16-week period following the viral infusion
- Use of immunosuppressive agents or live vaccines within 30 days before the viral infusion

2.4 Study Dosage and Administration

Each subject will receive a single IV injection of BMN 270 as an intravenous infusion. The volume of infusion will depend on the dose level:

1. 6E12 vector genomes [vg] per kilogram of body weight
2. 2E13 vg per kilogram
3. 6E13 vg per kilogram
4. 4E13 vg per kilogram

2.5 Sample Size Determination

No formal sample size calculations based on statistical power were performed. The sample size is determined based upon clinical considerations and the ability to detect a strong clinical efficacy signal.

Up to 15 subjects may be dosed in the study. The actual number of subjects will depend on the criteria for dose escalation.

2.6 Blinding and Randomization Methods

2.6.1 Blinding Method

Study 270-201 is an open-label study. No blinding will be performed.

2.6.2 Randomization Method

Study 270-201 is a dose escalation study. No randomization will be performed.

2.6.3 Interim Analysis

No formal interim analysis is planned. An analysis of the primary endpoint will be done following all subjects having completed the study assessments through the end of the Post-Infusion Follow-Up Period (Week 16).

3.0 GENERAL ANALYSIS CONSIDERATION

The subjects will be followed in a longitudinal manner, and all relevant information will be collected. The analysis of the data will be descriptive in nature. Descriptive statistics include subject count, mean, median, standard deviation, coefficient of variation, minimum, and maximum for continuous variables and count and percentage for categorical variables. The 95% confidence interval (CI) for the mean and the percentiles may also be included, if appropriate. Safety and efficacy variables will be summarized by dose cohort, and safety and efficacy results related to dose levels will be examined. Data collected in a longitudinal manner may be analyzed using longitudinal methods, such as mixed effect models, which take into account the correlation among the observations taken at various time points within a subject. Subgroup analyses may be performed, if appropriate.

3.1 Analysis Populations

3.1.1 Efficacy

The primary analysis population for efficacy analyses is the Full Analysis Set (FAS), defined as all enrolled subjects who receive BMN270 infusion and have at least one Baseline and post-Baseline assessment. The FAS will be used for efficacy analysis.

When applicable, additional efficacy sensitivity analyses will be carried out for the Per-Protocol (PP) analysis population, defined as a subset of the FAS who are compliant with the protocol and do not have major protocol violations that affect the interpretability of efficacy data. The PP population will be determined by team data review; reasons for excluding subjects will be defined and documented.

3.1.2 Safety

The Safety Analysis Population is defined as all enrolled subjects who receive BMN270 infusion. The analysis of safety data will be performed on Safety Analysis Population.

3.2 Treatment Group Presentation

In general, statistical summaries for each endpoint will be presented by BMN 270 dose levels subjects were assigned to (eg, 6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, 6E13 vg/kg) and overall.

3.3 Study Day Derivation

Study day is assigned as follows:

- The study drug infusion date is designated as Day 1.
- For visit days after Day 1, study day = visit date – Day 1 date + 1.
- For visit days prior to Day 1, study day = visit date − Day 1 date (Thus, study days for screening visits are negative numbers.)

3.4 Visit Windows for Analysis

Efficacy and safety data will be summarized by visit or by combining multiple visits based on windows defined in terms of study days, wherever applicable. Assessments will be assigned to derived visits according to the window into which the study day falls (Appendix 17.1). Unless stated otherwise, if there are two or more assessments within a designated window, the assessment that is closest to the target day will be used for analyses. If the two closest assessments to the target day are equidistant from the target day, then the mean of the two assessments will be used for analyses unless otherwise specified. If FVIII activity level is retested, the retest assessment will be used for the analyses.

3.5 Handling of Dropouts and Missing Data

If a subject withdraws from the study prior to the Week 260 visit, the subject will be asked to complete an Early Termination Visit (ETV).

Missing dates or partially missing dates will be imputed conservatively for concomitant medications and adverse events (AEs) to ensure that an AE is considered treatment emergent and the duration is the longest possible duration.

FVIII activity levels below the LLOQ (Lower limit of quantitation) will be imputed with 0 IU/dL.

Missing data will not be imputed unless otherwise stated. The main analyses will be observed cases (no imputation), in some cases supported by repeated measures approaches.

4.0 SUBJECT DISPOSITION

The number of subjects screened, number and percentage of screen failures by screen failure reasons will be summarized for all subjects screened. The number of subjects enrolled and the number and percentage by reason for subjects enrolled but not treated will be provided.

5.0 DISCONTINUATION AND COMPLETION

For treated subjects who prematurely discontinue study participation prior to the Week 26 visit, prior to the Week 52 visit and overall, the primary reason for discontinuation will be summarized by dose cohort.

The number and percentage of subjects who are continuing the study, who completed Week 104, and who completed Week 156 will also be provided for all treated subjects overall and by dose cohort.

6.0 PROTOCOL DEVIATIONS

The trial's Study Specific Guideline for Managing Protocol Deviations defines protocol deviations, including whether they are minor or major. Major protocol deviations will be summarized overall and by category for each dose cohort. A data listing of protocol deviations will be provided as well.

7.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be summarized include

- age at enrollment (year)
- age group (>=18-<30, >=30-<50, >=50)
- sex (Female/Male)
- ethnicity
- race
- height (cm)
- weight (kg)
- BMI (kg/m^2)
- Baseline ECG evaluation
- history of liver disease (Yes/No)
- history of hepatitis B (Yes/No)
- history of hepatitis C (Yes/No)
- history of HIV (Yes/No)
- baseline disease characteristics including:
    - time since diagnosis of hemophilia A (year)
    - type of FVIII treatment for hemophilia A (prophylaxis/on demand)
    - history of FVIII inhibitor (Yes/No)
    - number of target joints
    - body location of target joints
    - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL)
- duration of baseline data collection periods, months
- baseline annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy
- baseline annualized number of FVIII infusions (infusions/year)

- baseline ABR (bleeds/year)

8.0 MEDICAL HISTORY

Medical history will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) at the time of coding. Medical history will be summarized by system organ class (SOC) and preferred term (PT).

9.0 PRIOR AND CONCOMITANT MEDICATIONS/PROCEDURES

Prior and concomitant medications are defined as follows:

- prior medication—any medication taken prior to the initiation of the investigational product and within 30 days prior to screening;
- concomitant medication—any medication taken after the initiation of the investigational product.

When a medication starts prior to the initiation of the investigational product and continues while on study, it will be summarized as both prior and concomitant medications.

All medications will be coded using the current version of the World Health Organization Drug (WHO Drug) Dictionary.

Prior and concomitant medication use will be separately summarized by Anatomical Therapeutic Chemical (ATC) medication class (Level 4) and preferred name (i.e., generic medication name). A subject reporting the same medication more than once will be counted once when calculating the number and percentage of subjects who received that medication.

Corticosteroid usage including total dose and total duration per subject, dose per use, duration per use, and time to corticosteroid use will be summarized overall and by for therapeutic and prophylactic purposes.

10.0 EXTENT OF EXPOSURE TO STUDY DRUG

Each subject will receive a single IV injection of BMN 270, and the volume of infusion will depend on the dose level and subject weight. Study drug dosing compliance will be assessed by providing descriptive summaries of actual dose, and number of administered study drug infusions below the planned dose. The follow-up time of each subject will be summarized descriptively.

A data listing of drug exposure will be provided.

11.0 EFFICACY EVALUATIONS

This section describes the analyses to be undertaken for the primary, secondary, and other efficacy variables. Efficacy at week 16 after BMN 270 infusion will be analyzed. Long-term efficacy based on data including but not exclusive to week 26, week 52, and up to 5 years post-BMN 270 dosing will be evaluated.

As it is expected to take four weeks for the endogenous production of FVIII following gene transfer to be efficacious, for the purpose of data review and interpretation, the efficacy period will be defined as

starting from week 5 post-BMN 270 dosing until subjects resume routine FVIII prophylaxis, should that occur before the end of the safety long term follow up or ETV, whichever is earlier.

11.1 Primary Efficacy Endpoint(s)

Plasma FVIII activity will be determined by validated assays, one-stage clotting and chromogenic substrate assays, assessed by the central lab. Plasma FVIII activity will be assessed weekly for 36 weeks after BMN 270 infusion and continue to have the regularly scheduled assessments as planned in the protocol. The true steady-state of plasma FVIII activity level produced from BMN 270 can only be assessed after a minimum of 72 hours has elapsed since the last infusion of FVIII protein concentrates. Therefore, FVIII activity levels within 72-hours after FVIII use will be excluded from analysis. FVIII activity levels below the LLOQ (Lower limit of quantitation) will be imputed with 0 IU/dL. If FVIII activity level is retested, the retest assessment will be used for all analyses. A listing of original test assessment and retest assessment will be provided.

The primary efficacy endpoints will be:

- Responder/nonresponder status, where a responder is defined as a subject with median FVIII activity of ≥ 5 IU/dL during week 13-16 post-BMN 270 infusion
- Median FVIII activity during week 13-16

11.1.1 Primary Analysis Method

The number and percentage of subjects with median FVIII activity ≥ 5 IU/dL during week 13-16 will be summarized for each dose cohort.

Median FVIII activity during week 13-16 will be summarized descriptively by dose cohort.

Median FVIII activity over time will be summarized descriptively by dose cohort every 4 weeks up to week 104 and every 6 weeks afterwards. The visits and visit windows are defined in Appendix 17.1. Each subject's FVIII activity level in a visit window is defined as the median of the values obtained during the window. Corresponding boxplots of median FVIII activity levels at every 4-week or 6-week interval over time will be provided by cohort.

Individual subject plasma FVIII activity assessments will be presented in plots and listings:

- A bar plot of individual subject median FVIII activity during week 13-16 will be created.
- Individual subject profile plots of FVIII activity assessments over time together with other key efficacy and safety endpoints, including bleeding episodes and corresponding exogenous FVIII use, ALT assessments, glucocorticoid treatment, and prophylactic glucocorticoid treatment will also be presented.
- Line plots ("spaghetti plots") of subject FVIII activity assessments versus study day will be provided by cohort.

The primary analyses will be conducted for both the one-stage clotting and chromogenic substrate assays for the FAS analysis population. The above analyses will be conducted for long-term efficacy data if

needed, e.g., similar analyses may be performed at week 26, week 52, and up to 5 years-post BMN 270 dosing.

11.1.2 Supportive Analysis Methods

The distribution of median FVIII activity level during week 13-16 will be further explored with cumulative distribution function (CDF) plots: the horizontal axis represents the continuum of values of plasma FVIII activity (IU/dL), and the vertical axis shows the percentage of subjects achieving at least that level of activity. Thus, a CDF plot shows the percentage of subjects achieving each level of response. Applying different thresholds along the CDF curve allows interpretation of the curve at various levels of response. Thresholds of particular interest include 5, 15, 25, 30 and 40 IU/dL. The summary of corresponding responder analyses will also be provided.

The distribution of time from infusion to FVIII activity level first achieving 5 IU/dL and the duration of maintaining FVIII activity between levels of 5-150 IU/dL (excluding the time periods when FVIII activity level drops below 5 IU/dL or increases above 150 IU/dL) until Week 16 will also be explored by cohort. The distribution of duration of FVIII activity remaining under 1 IU/dL, between 1-5 IU/dL and above 150 IU/dL may be explored by cohort, if needed.

The intra-subject and inter-subject variability in FVIII activity before and/or after subjects reach steady state may be explored using descriptive statistics and model-based methods.

The supportive analyses will be conducted for the FAS analysis population. The same analyses will be conducted for long-term efficacy data if needed.

11.1.3 Sensitivity Analysis Methods

The analyses described above may be repeated for the PP analysis population if applicable.

To investigate the robustness of the primary analysis, which uses the median FVIII activity value if more than one assessments falls within an analysis window, a sensitivity analysis may be performed using the mean of the multiple assessments.

To investigate the relationship between the FVIII activities by one-stage clotting and chromogenic substrate assays, a regression analysis to fit both assays to a regression line will be conducted.

11.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints are:

Annualized bleeding rate (ABR) (counts/yr.)

$$= \frac{\text{Number of bleeding episodes during calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

Annualized FVIII use (IU/kg/yr.)

$$= \frac{\text{Sum of FVIII use(IU/kg) during calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

Annualized FVIII infusion rate (count/yr.)

$$= \frac{\text{Number of FVIII replacement infusions during calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

Subjects will be asked at each study visit to report the number of bleeding episodes and the use of factor replacement therapy since the previous visit. This information will be captured on the subject's diary or other subject records. A bleeding episode is defined as a bleed or symptoms associated with the development of a bleed (or multiple bleeds occurred in the same day) requiring FVIII replacement treatment.

The calculation period in the above formulas for post-baseline values will be Weeks 1-4, Weeks 5-26, Weeks 5-52, and Weeks 5 and beyond.

The baseline values for the secondary endpoints will be based on the historical data prior to study enrollment.

The ABR by individual subject and ABR descriptive statistics over time (pre-infusion and post-infusion calculation periods) by cohort will be tabulated. Such tabulation may also be performed for subgroups defined by baseline FVIII treatment regimen (on-demand vs. prophylaxis). The same tabulation will be performed for ABR before FVIII activity achieving 5 IU/dL and ABR after FVIII activity achieving 5 IU/dL. The ABR change from pre-infusion will be summarized by cohort. Summaries by the bleeding site (target joint, non-target joint), bleeding cause (spontaneous, traumatic), by cohort may also be performed for ABR. Scatter plots of post-infusion individual bleeding episodes over time will be plotted. A comparison of pre-infusion and post-infusion ABR using Poisson regression model followed by a test for overdispersion will be performed. The ABR will be analyzed using negative binomial regression if overdispersion exists. A comparison using a Wilcoxon signed-rank test may also be performed.

The above ABR analyses will be repeated for treated bleeds, as defined using standard criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Hemostasis. A bleed is considered to be a "treated bleed" if it is directly followed by a haemophilia medication reported to be a "treatment for bleeding episode" irrespective of the time between the treatment and the preceding bleed (i.e., there is not an intervening bleed). A bleed and the first treatment thereafter are considered to be pairs (i.e., one treatment belongs to one bleed only), with the following exception: if multiple bleeds occur on the same calendar day, the subsequent treatment is considered to apply for each of these multiple bleeds (which are, however, counted as separate treated bleeds). Bleeds due to surgery/procedure are not included in the primary analysis. Only treatments that were recorded as "treatment for bleeding episode" are included in the determination of a treated bleed. Two bleeds at the same anatomical location are considered to be 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. This is in line with the above definition that bleeds and treatments are considered to be pairs.

The Annualized FVIII use and Annualized FVIII infusion rate will be analyzed similarly as ABR. The post-infusion and pre-infusion annualized FVIII use will be compared using a paired t-test. The FVIII replacement treatment by the following different categories will also be summarized:

- Treatment for adverse events (including all bleeds, and symptoms associated with the development of a bleed or bruises that would occur in a non-haemophiliac person per protocol)
- Treatment for bleeding episode (including all bleeds, and symptoms associated with the development of a bleed or bruises that are normal events of haemophilia but should not be treated as AEs per protocol)
- Prophylaxis (routine)
- Surgery/procedure
- Prophylaxis (precautionary due to activity/injury)

The analyses described for the secondary endpoints will be conducted for the FAS analysis population. Sensitivity analyses using PP analysis population may be performed for secondary endpoints, if applicable.

11.2.1 Correlation between FVIII Activity and Bleeding Risk

FVIII activity is widely acknowledged to be a key aspect of hemophilia A and a valuable indicator of patients' status, while annualized bleeding rate has been traditionally used as the primary clinical endpoint for replacement therapy. The correlation between FVIII activity level and bleeding risk has been researched, showing that increases in FVIII activity levels are predictably associated with a decreased number of annual bleeds (Den Uijl, 2011, Haemophilia). The following analyses will be performed to explore the relationship between measured FVIII activity and bleeding in this study.

- Based on the FVIII activity visit windows (Appendix 1), median FVIII activity and total number of treated bleeds (defined in Section 11.2) will be calculated for each window for every subject. A negative binomial regression will be performed, modelling number of bleeds in each window vs. FVIII activity in the window. The analysis will be done for FVIII activity measured by one-stage clotting assay and chromogenic assay separately. The same analyses will be conducted for treated joint bleeds. The analysis will use observed cases and be performed for the Full Analysis Set.
- Using a cutoff of FVIII activity level, e.g., 40 IU/dL, each subject's data will be divided into 2 periods: from Week 5 to the first time reaching 40 IU/dL, and from the first time reaching 40 IU/dL to the end of efficacy period. For each period, the duration of the period, the number of bleeds, the ABR, and the change in ABR from baseline will be listed and summarized. The analysis will be performed using various cutoffs, such as 5, 15, 25, 30, 40 IU/dL.

11.3 Other Efficacy Endpoint(s)

The Haemo-QoL-A is a patient-reported outcome (PRO) questionnaire which will be used to assess subject quality of life (QoL) during the study. Change from Baseline will be summarized for the total score and subscale scores (physical functioning, role functioning, worry, consequences of bleeding, emotional impact, treatment concern). Graphic summary of mean QoL change over time will be provided

for the total score and each subscale scores. Mixed model for repeated measures (MMRM) may be performed to analyze the change from baseline in PROs. The 95% CIs of the mean changes may be provided.

FVIII activity by both one-stage clotting and chromogenic substrate assays will also be assessed at local labs at the same time points as when they will be by the central lab. A data listing of local FVIII activity assessments will be provided. The analyses for central FVIII activity assessments will be conducted, if needed.

The analyses described in this section will be conducted for the FAS.

11.4 Examination of Efficacy by Subgroups

The following subgroup analyses may be examined for key efficacy endpoints by dose cohort:

- Baseline FVIII treatment regimen: On-demand vs. prophylactic therapy
- Baseline Age: 18-29 years vs. 30-50 years vs. >50 years old
- Race
- History of target joint(s)

These analyses will be conducted for the FAS analysis population.

12.0 SAFETY EVALUATIONS

Safety will be assessed by adverse event reporting; clinical laboratory assessments, with particular attention to liver tests; vital signs assessments; physical examinations; and immunogenicity. Safety analyses will be carried out for the Safety analysis population. No formal statistical testing will be performed; only summary statistics will be provided, unless otherwise noted.

12.1 Adverse Events

Only treatment-emergent adverse events (TEAEs) occurring and reported during the study period will be included in the adverse event summaries. A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug administration. Adverse events will be coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA).

An adverse drug reaction (ADR) is any AE for which there is a reasonable possibility that the study drug caused the AE. The investigator will assess the causality for individual AEs, applying the guidance specified in protocol, and those assessed as study drug-related will be considered ADRs.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets one or more of the seriousness criteria enumerated in the protocol. AE severity, not equivalent to seriousness, will be assessed using the protocol defined categories using the NCI CTCAE v4.03.

All bleeding events and suspected bleeding events, regardless of the need for exogenous FVIII therapy as treatment, should be captured in subject diaries and recorded on the designated bleeding eCRF. Bleeding

events and suspected bleeding events should not be reported as adverse events, with the following exception:

- All bleeding events and suspected bleeding events which meet one or more of the criteria for being serious (refer to protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of haemophilia, and whether or not they required exogenous FVIII as treatment).

The study AE reporting period is as follows: After informed consent but prior to initiation of study treatment, only SAEs associated with any protocol-imposed interventions will be reported. After informed consent is obtained and the administration of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is later.

The following types of AEs will be summarized: all AEs, AEs assessed by investigator as related, SAEs, SAEs assessed by investigator as related, AEs leading to study discontinuation, deaths, EOSIs. Listings will be provided.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 3.5will be applied.

12.1.1 All Adverse Events

The incidence and number of events for all TEAEs will be summarized by system organ class (SOC), preferred term (PT) and severity for each dose cohort and overall. For those AEs that occurred more than once during the study, the maximum severity will be used to summarize the AEs by severity. In addition to TEAE listing, a listing of AEs reported under Investigations SOC will also be provided.

12.1.2 Drug-Related Adverse Events

All TEAEs assessed by investigator as study drug related (ADR) will be summarized by SOC, PT and severity for each dose cohort and overall.

12.1.3 Deaths and Serious Adverse Events

Serious adverse events and SAEs assessed by investigator as study drug related (serious ADR) will be summarized by SOC, PT and severity for each dose cohort and overall. A list of subjects who died and all SAEs will be provided.

12.1.4 Adverse Events Causing Early Discontinuation

Adverse events that cause early discontinuation of study will be summarized by SOC, PT and severity for each dose cohort and overall if needed. In addition, a list of subjects with the AEs resulting in discontinuation of study will be provided.

12.1.5 Events of Interest

The following events of interest, which include EOSI defined in the protocol, will be summarized by PT, if applicable. A list of subjects will be provided for each type of EOSI. AE profile summary including time

to event onset from infusion and duration of the events will be generated for EOSI (unless otherwise specified below).

- Transaminitis
  - ALT elevation reported as EOSIs (Preferred term: "Alanine aminotransferase increased", reported as EOSI).
  - AEs of liver dysfunction, defined using the MedDRA search strategy high level term (HLT = "Liver function analyses").
  - Potential Hy's law cases
    - ALT or AST ≥ 3x ULN and serum TBL > 2x ULN
    - Assessments of ALT/AST and TBL must be on the same day

    A listing will be provided.
- Infusion related reaction, Hypersensitivity, Anaphylactic or Anaphylactic reactions
  - Infusion related reactions, defined as AEs occurring during BMN 270 infusion or within 48 hours post-infusion, will be summarized as follows:
    - Subjects who receive infusion with initial rate of approximately 4 mL/min
    - The rest of the subjects, i.e. subjects who receive infusion with initial rate of 1 mL/min
    - All treated subjects
  - Systemic hypersensitivity (Hypersensitivity [SMQ] – narrow scope).
  - Anaphylactic, or anaphylactoid reactions (Anaphylactic reaction [SMQ] – algorithmic) – listing only.
- Thromboembolic events:
  - Embolic and thrombotic events (SMQ) for entire study period.
  - AEs suggestive of thromboembolic events: for subjects who have FVIII elevation > 150% any time during study, a listing of clinical terms suggestive of thromboembolic events observed from the time point prior to when FVIII was elevated until FVIII falls below 150%. (The preferred terms are listed in Appendix 17.2.)
- Development of anti-FVIII Inhibitors as measured by Nijmegen modified Bethesda Assay (Preferred term: "Anti factor VIII antibody positive")

12.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, haematology, urine tests, CRP and coagulation. Clinical laboratory test values and change from Baseline will be summarized descriptively by visit for each dose cohort and overall. Shift tables cross-tabulating CTCAE v4.03 grade at Baseline vs. worst CTCAE v4.03

grade at post-Baseline visits will be provided as well. A supportive listing of abnormal test values with CTCAE v4.03 grade 3 or greater will be produced.

Liver tests (LTs) by central labs will be assessed on a regular basis, as detailed in the protocol. Boxplots of maximum ALT values at 4-week intervals over time and corresponding line plots will be provided by cohort. The same analyses based on mean or median ALT values may be conducted. ALT values and change from Baseline over time will be summarized descriptively by dose cohort. Summaries of ALT elevations including baseline ALT, time from infusion to ALT > ULN, ALT > 3x ULN, ALT > 5x ULN, ALT ≥ 1.5x ULN or (> ULN & > 2x baseline value), peak ALT level, duration of ALT elevation will be provided. Correlation of ALT elevation to FVIII levels, as well correlation of steroid treatment to ALT elevation and FVIII levels will be examined using subjects' profile figures. Local ALT assessments will be analyzed similarly as the central ALT assessments, if needed. Similar analyses will be applied to other liver tests including aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, and alkaline phosphatase (ALP), if needed.

In addition, incidence of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law, will be summarized by count and percentage. The profile summary of the related laboratory tests results needed for determination by Hy's law will be provided for the subjects with potential DILI.

12.3 Vital Signs and Physical Examination

Vital signs variables include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature. Vital signs will be summarized descriptively by visit. Physical examinations will include assessments of general appearance; head, eyes, ears, nose, and throat; the cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. Physical examination results (normal or abnormal) will be summarized descriptively by visit.

12.4 Electrocardiogram, Chest X-Ray and Liver Ultrasound

Electrocardiogram (ECG), chest X-ray and liver ultrasound are performed at the Screening visit with additional evaluations to be performed if clinically indicated during the study. Test results (normal, abnormal, or unknown) will be summarized or provided in data listings, as appropriate for the amount of data collected.

12.5 Viral Shedding

Viral shedding will be extensively studied at Baseline visit and every other week between week 4-16, then every 4 weeks to week 52 until at least 3 consecutive negative results are obtained. Testing of semen will continue through week 12, even if 3 consecutive negative results have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive negative samples by week 52 should continue to have PCR testing every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Body fluids including blood, saliva, semen, urine and stool will be tested by PCR at the time points.

The vector genomes tested in extracted body samples will be summarized by visit in tabular and/or graphical format. In addition, the number (%) of patients with detectable vector genomes by visit and sample type, the duration of shedding by sample type, and the peak period(s) of shedding by sample type will be summarized. Values below the LLOQ will be imputed as one half of the validated LLOQ of 50 vg/q PCR and back calculated to the theoretically corresponding genome amounts per standard unit of biospecimen.

13.0 IMMUNOGENICITY ASSESSMENT

Analysis of immunological parameters will be primarily descriptive. Assays to detect pre-existing immunogenicity specific for AAV5, including plasma derived inhibitors of transduction (transduction inhibition or TI) and total antibody (TAb) assays, will be tested at the Screening visit before BMN 270 infusion is given and at post-baseline visits according to the protocol's schedule of events. Test results (negative and positive with titer) will be summarized or provided in data listings, as appropriate for the amount of data collected.

Two assays are in place to determine immunogenicity to the human FVIII transgene product. The first is a total antibody (TAb) assay to detect binding antibodies in patient plasma directed against human FVIII and is reported as negative or positive with titer. The second is to evaluate neutralizing antibodies (NAb) capable of interfering with FVIII activity (FVIII Inhibitors) and is determined using the Bethesda assay with Nijmegen modification. This assay is reported out in Bethesda Units (BU), with a value of <0.6 considered negative. Both assays will be performed on patient plasma samples obtained at the screening visit, and at post-baseline visits according to the protocol's schedule of events. Test results will be summarized or provided in data listings as appropriate for the amount of data collected. The associations between antibody responses and the occurrence of adverse events or other safety or efficacy endpoints such as bleeding rate, FVIII activity values and clinical chemistries may be explored.

Cellular immunity in the form of cytotoxic T lymphocytes (CTL) will be evaluated by Interferon-gamma (IFN- γ) ELISpot assay of peripheral blood mononuclear cells (PBMC). PBMC will be stimulated with overlapping peptide pools derived from the AAV5 capsid protein or human FVIII protein sequences to evaluate IFN- γ secretion by CTL targeting both the AAV5 capsid and the FVIII transgene product. Cellular immunity will be evaluated at baseline and at post-infusion visits according to the protocol's schedule of events and is reported positive or negative by peptide pool stimulation and as spot forming units (SFU) per 10^6 PBMC. A data listing will be generated reporting positive or negative and the number of SFU 10^6 PBMC for each peptide pool and control (positive and negative) stimulation for each patient at each study visit tested. Positive and negative results with the number of SFU per 10^6 PBMC will be evaluated for correlations with FVIII activity measures, changes in clinical chemistry or adverse events as appropriate for the data collected.

14.0 CLINICAL PHARMACOLOGY

Clinical pharmacology analyses will be specified in a separate clinical pharmacology analysis plan.

15.0 REFERENCES

Den Uijl, IE, Mauser Bunschoten, EP, Roosendaal, G, Schutgens, RE et al. Clinical severity of haemophilia A: does the classification of the 1950s still stand? Haemophilia 17[6], 849-853. 2011.

ICH, E9. Statistical principles for clinical trials. 1998.

16.0 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	11OCT2017		Initial version
2.0	10DEC2018	Most sections	Revision to reflect updates in the protocol amendment and to be consistent with 301 SAP.
3.0	15May2019	Multiple	Revision to reflect updates in the protocol amendment and definition of EOSI.

17.0 APPENDICES

17.1 Appendix 1. Visit Windows

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
FVIII activity[d], Liver tests	Baseline[c]	Day -7 – Day -1	≤ Day 1
	Week 1 - 4		Days [2, 32]
	Week 5 - 8		Days [33, 60]
	Week 9 - 12		Days [61, 88]
	Week 13 - 16		Days [89, 116]
	Week 17 - 20		Days [117, 144]
	Week 21 - 24		Days [145, 172]
	Week 23 – 26		Days [159, 186]
	Week 25 - 28		Days [173, 200]
	Week 29 - 32		Days [201, 228]
	Week 33 - 36		Days [229, 256]
	Week 37 - 40		Days [257, 284]
	Week 41 - 44		Days [285, 312]
	Week 45 - 48		Days [313, 340]
	Week 49 - 52		Days [341, 368]
	Week 56	Day 393	Days [369, 406]
	Week 60	Day 421	Days [407, 434]
	Week 64	Day 449	Days [435, 462]
	Week 68	Day 477	Days [463, 490]
	Week 72	Day 505	Days [491, 518]
	Week 76	Day 533	Days [519, 546]
	Week 80	Day 561	Days [547, 574]
	Week 84	Day 589	Days [575, 602]
	Week 88	Day 617	Days [603, 630]
	Week 92	Day 645	Days [631, 658]
	Week 96	Day 673	Days [659, 686]
	Week 100	Day 701	Days [687, 714]
	Week 104	Day 729	Days [715, 742]

	Week 110	Day 771	Days [743, 791]
	Week 116	Day 813	Days [792, 833]
	Week 122	Day 855	Days [834, 875]
	Week 128	Day 897	Days [876, 917]
	Week 134	Day 939	Days [918, 959]
	Week 140	Day 981	Days [960, 1001]
	Week 146	Day 1023	Days [1002, 1043]
	Week 152	Day 1065	Days [1044, 1085]
	Week 158	Day 1107	Days [1086, 1127]
	Week 164	Day 1149	Days [1128, 1169]
	Week 170	Day 1191	Days [1170, 1211]
	Week 176	Day 1233	Days [1212, 1253]
	Week 182	Day 1275	Days [1254, 1295]
	Week 188	Day 1317	Days [1296, 1337]
	Week 194	Day 1359	Days [1338, 1379]
	Week 200	Day 1401	Days [1380, 1421]
	Week 206	Day 1443	Days [1422, 1463]
	Week 212	Day 1485	Days [1464, 1505]
	Week 218	Day 1527	Days [1506, 1547]
	Week 224	Day 1569	Days [1548, 1589]
	Week 230	Day 1611	Days [1590, 1631]
	Week 236	Day 1653	Days [1632, 1673]
	Week 242	Day 1695	Days [1674, 1715]
	Week 248	Day 1737	Days [1716, 1757]
	Week 254	Day 1779	Days [1758, 1799]
	Week 260	Day 1821	Days [1800, 1841]
Note: median or mean of the assessments within the above windows will be used for analysis.			
Bleeds, FVIII use, ABR, Annualized FVIII use	Baseline		< Day 1
	Week 1 - 4		Days [1, 32]
	Week 5 - 26		Days [33, 186]
	Week 5 - 52		Days [33, 368]

	Week 5 and Beyond		≥ Day 33
Note: all assessments within the above defined windows will be used to derive the corresponding endpoint.			
Haemo-QoL-A quality of life	Baseline	Day -7 to Day -1	≤ Day 5
	Week 1	Day 8	Days [6,11]
	Week 2	Day 15	Days [12, 18]
	Week 3	Day 22	Days [19, 25]
	Week 4	Day 29	Days [26, 70]
	Week 16	Day 113	Days [71, 154]
	Week 28	Day 197	Days [155, 280]
	Week 52	Day 365	Days [281, 448]
	Week 76	Day 533	Days [449, 630]
	Week 104	Day 729	Days [631, 812]
	Week 128	Day 897	Days [813, 994]
	Week 156	Day 1093	Days [995, 1176]
	Week 180	Day 1261	Days [1177, 1358]
	Week 208	Day 1457	Days [1359, 1540]
	Week 232	Day 1625	Days [1541, 1722]
	Week 260	Day 1821	Days [1723, 1904]
PCR vector genomes (blood, saliva, urine, semen, stools)[e]	Baseline [c]	Day -7 to Day -1	Days ≤ 1
	Day 2	Day 2	Days [2]
	Day 4	Day 4	Days [3,5]
	Day 8	Day 8	Days [6,18]
	Week 4	Day 29	Days [19, 35]
	Week 6	Day 43	Days [36, 49]
	Week 8	Day 57	Days [50, 63]
	Week 10	Day 71	Days [64, 77]
	Week 12	Day 85	Days [78, 91]

	Week 14	Day 99	Days [92, 105]
	Week 16	Day 113	Days [106, 126]
	Week 20	Day 141	Days [127, 154]
	Week 24	Day 169	Days [155, 182]
	Week 28	Day 197	Days [183, 210]]
	Week 32	Day 225	Days [211, 238]
	Week 36	Day 253	Days [239, 266]
	Week 40	Day 281	Days [267, 294]
	Week 44	Day 309	Days [295, 322]
	Week 48	Day 337	Days [323, 350]
	Week 52	Day 365	Days [351, 378]
	Week 56	Day 393	Days [379, 406]
	Week 60	Day 421	Days [407, 434]
	Week 64	Day 449	Days [435, 462]
	Week 68	Day 477	Days [463, 490]
	Week 72	Day 505	Days [491, 518]
	Week 76	Day 533	Days [519, 546]
	Week 80	Day 561	Days [547, 574]
	Week 84	Day 589	Days [575, 602]
	Week 88	Day 617	Days [603, 630]
	Week 92	Day 645	Days [631, 658]
	Week 96	Day 673	Days [659, 686]
	Week 100	Day 701	Days [687, 714]
	Week 104	Day 729	Days [715, 742]
	Week 110	Day 771	Days [743, 791]
	Week 116	Day 813	Days [792, 833]
	Week 122	Day 855	Days [834, 875]
	Week 128	Day 897	Days [876, 917]
	Week 134	Day 939	Days [918, 959]
	Week 140	Day 981	Days [960, 1001]
	Week 146	Day 1023	Days [1002, 1043]

	Week 152	Day 1065	Days [1044, 1085]
	Week 158	Day 1107	Days [1086, 1127]
	Week 164	Day 1149	Days [1128, 1169]
	Week 170	Day 1191	Days [1170, 1211]
	Week 176	Day 1233	Days [1212, 1253]
	Week 182	Day 1275	Days [1254, 1295]
	Week 188	Day 1317	Days [1296, 1337]
	Week 194	Day 1359	Days [1338, 1379]
	Week 200	Day 1401	Days [1380, 1421]
	Week 206	Day 1443	Days [1422, 1463]
	Week 212	Day 1485	Days [1464, 1505]
	Week 218	Day 1527	Days [1506, 1547]
	Week 224	Day 1569	Days [1548, 1589]
	Week 230	Day 1611	Days [1590, 1631]
	Week 236	Day 1653	Days [1632, 1673]
	Week 242	Day 1695	Days [1674, 1715]
	Week 248	Day 1737	Days [1716, 1757]
	Week 254	Day 1779	Days [1758, 1799]
	Week 260	Day 1821	Days [1800, 1841]
FVIII antibody positivity/titer	Baseline[c]	Day -7 to Day -1	Days ≤ 1
	Week 4	Day 29	Day [2, 42]
	Week 8	Day 57	Day [43, 70]
	Week 12	Day 85	Day [71, 98]
	Week 16	Day 113	Day [99, 126]
	Week 20	Day 141	Day [127, 154]
	Week 28	Day 197	Day [155, 224]
	Week 36	Day 253	Day [225, 280]
	Week 44	Day 309	Day [281, 336]
	Week 52	Day 365	Day [337, 410]
	Week 65	Day 456	Day [411, 501]

	Week 78	Day 547	Day [502, 592]
	Week 91	Day 638	Day [593, 683]
	Week 104	Day 729	Day [684, 774]
	Week 117	Day 820	Day [775, 865]
	Week 130	Day 911	Day [866, 956]
	Week 143	Day 1002	Day [957, 1047]
	Week 156	Day 1093	Day [1048, 1138]
	Week 169	Day 1184	Day [1139, 1229]
	Week 182	Day 1275	Day [1230, 1320]
	Week 195	Day 1366	Day [1321, 1411]
	Week 208	Day 1457	Day [1412, 1502]
	Week 221	Day 1548	Day [1503, 1593]
	Week 234	Day 1639	Day [1594, 1684]
	Week 247	Day 1730	Day [1685, 1775]
	Week 260	Day 1821	Day [1776, 1835]
Clinical Laboratory tests (Blood chemistry, Haematology, Coagulation, CRP, AAV5 antibody, Urine[f])	Baseline[c]	Day -7 to Day -1	Days ≤ 1
	Week 2	Day 15	Days [2, 21]
	Week 4	Day 29	Days [22, 35]
	Week 6	Day 43	Days [36, 49]
	Week 8	Day 57	Days [50, 63]
	Week 10	Day 71	Days [64, 77]
	Week 12	Day 85	Days [78, 98]
	Week 16	Day 113	Days [99, 126]
	Week 20	Day 141	Days [127, 154]
	Week 24	Day 169	Days [155, 182]
	Week 28	Day 197	Days [183, 210]
	Week 32	Day 225	Days [211, 238]
	Week 36	Day 253	Days [239, 266]
	Week 40	Day 281	Days [267, 294]
	Week 44	Day 309	Days [295, 322]

	Week 48	Day 337	Days [323, 350]
	Week 52	Day 365	Days [351, 410]
	Week 65	Day 456	Day [411, 501]
	Week 78	Day 547	Day [502, 592]
	Week 91	Day 638	Day [593, 683]
	Week 104	Day 729	Day [684, 774]
	Week 117	Day 820	Day [775, 865]
	Week 130	Day 911	Day [866, 956]
	Week 143	Day 1002	Day [957, 1047]
	Week 156	Day 1093	Day [1048, 1138]
	Week 169	Day 1184	Day [1139, 1229]
	Week 182	Day 1275	Day [1230, 1320]
	Week 195	Day 1366	Day [1321, 1411]
	Week 208	Day 1457	Day [1412, 1502]
	Week 221	Day 1548	Day [1503, 1593]
	Week 234	Day 1639	Day [1594, 1684]
	Week 247	Day 1730	Day [1685, 1775]
	Week 260	Day 1821	Day [1776, 1835]
PBMC	Baseline[c]	Day -7 to Day -1	Days ≤ 1
	Week 4	Day 29	Days [2, 32]
	Week 8	Day 57	Days [33, 60]
	Week 12	Day 85	Days [61, 88]
	Week 16	Day 113	Days [89, 116]
	Week 20	Day 141	Days [117, 144]
	Week 24	Day 169	Day [145, 172]
	Week 28	Day 197	Day [173, 228]
	Week 36	Day 253	Days [229, 284]
	Week 44	Day 309	Days [285, 340]
	Week 52	Day 365	Days [341, 410]
	Week 65	Day 456	Day [411, 501]

	Week 78	Day 547	Day [502, 592]
	Week 91	Day 638	Day [593, 683]
	Week 104	Day 729	Day [684, 774]
	Week 117	Day 820	Day [775, 865]
	Week 130	Day 911	Day [866, 956]
	Week 143	Day 1002	Day [957, 1047]
	Week 156	Day 1093	Day [1048, 1138]
	Week 169	Day 1184	Day [1139, 1229]
	Week 182	Day 1275	Day [1230, 1320]
	Week 195	Day 1366	Day [1321, 1411]
	Week 208	Day 1457	Day [1412, 1502]
	Week 221	Day 1548	Day [1503, 1593]
	Week 234	Day 1639	Day [1594, 1684]
	Week 247	Day 1730	Day [1685, 1775]
	Week 260	Day 1821	Day [1776, 1835]
FVIII inhibitor, FVIII antigen	Baseline[c]	Day -7 – Day -1	≤ Day 1
	Week 1	Day 8	Days [2, 11]
	Week 2	Day 15	Days [12, 18]
	Week 3	Day 22	Days [19, 25]
	Week 4	Day 29	Days [26, 32]
	Week 5	Day 36	Days [33, 39]
	Week 6	Day 43	Days [40, 46]
	Week 7	Day 50	Days [47, 53]
	Week 8	Day 57	Days [54, 60]
	Week 9	Day 64	Days [61, 67]
	Week 10	Day 71	Days [68, 74]
	Week 11	Day 78	Days [75, 81]
	Week 12	Day 85	Days [82, 88]
	Week 13	Day 92	Days [89, 95]
	Week 14	Day 99	Days [96, 102]

	Week 15	Day 106	Days [103, 109]
	Week 16	Day 113	Days [110, 116]
	Week 17	Day 120	Days [117, 123]
	Week 18	Day 127	Days [124, 130]
	Week 19	Day 134	Days [131, 137]
	Week 20	Day 141	Days [138, 144]
	Week 21	Day 148	Days [145, 151]
	Week 22	Day 155	Days [152, 158]
	Week 23	Day 162	Days [159, 165]
	Week 24	Day 169	Days [166, 172]
	Week 25	Day 176	Days [173, 179]
	Week 26	Day 183	Days [180, 186]
	Week 27	Day 190	Days [187, 193]
	Week 28	Day 197	Days [194, 200]
	Week 29	Day 204	Days [201, 207]
	Week 30	Day 211	Days [208, 214]
	Week 31	Day 218	Days [215, 221]
	Week 32	Day 225	Days [222, 228]
	Week 33	Day 232	Days [229, 235]
	Week 34	Day 239	Days [236, 242]
	Week 35	Day 246	Days [243, 249]
	Week 36	Day 253	Days [250, 259]
	Week 38	Day 267	Days [260, 273]
	Week 40	Day 281	Days [274, 287]
	Week 42	Day 295	Days [288, 301]
	Week 44	Day 309	Days [302, 315]
	Week 46	Day 323	Days [316, 329]
	Week 48	Day 337	Days [330, 343]
	Week 50	Day 351	Days [344, 357]
	Week 52	Day 365	Days [358, 371]
	Week 56	Day 393	Days [372, 406]

	Week 60	Day 421	Days [407, 434]
	Week 64	Day 449	Days [435, 462]
	Week 68	Day 477	Days [463, 490]
	Week 72	Day 505	Days [491, 518]
	Week 76	Day 533	Days [519, 546]
	Week 80	Day 561	Days [547, 574]
	Week 84	Day 589	Days [575, 602]
	Week 88	Day 617	Days [603, 630]
	Week 92	Day 645	Days [631, 658]
	Week 96	Day 673	Days [659, 686]
	Week 100	Day 701	Days [687, 714]
	Week 104	Day 729	Days [715, 742]
	Week 110	Day 771	Days [743, 791]
	Week 116	Day 813	Days [792, 833]
	Week 122	Day 855	Days [834, 875]
	Week 128	Day 897	Days [876, 917]
	Week 134	Day 939	Days [918, 959]
	Week 140	Day 981	Days [960, 1001]
	Week 146	Day 1023	Days [1002, 1043]
	Week 152	Day 1065	Days [1044, 1085]
	Week 158	Day 1107	Days [1086, 1127]
	Week 164	Day 1149	Days [1128, 1169]
	Week 170	Day 1191	Days [1170, 1211]
	Week 176	Day 1233	Days [1212, 1253]
	Week 182	Day 1275	Days [1254, 1295]
	Week 188	Day 1317	Days [1296, 1337]
	Week 194	Day 1359	Days [1338, 1379]
	Week 200	Day 1401	Days [1380, 1421]
	Week 206	Day 1443	Days [1422, 1463]
	Week 212	Day 1485	Days [1464, 1505]
	Week 218	Day 1527	Days [1506, 1547]

	Week 224	Day 1569	Days [1548, 1589]
	Week 230	Day 1611	Days [1590, 1631]
	Week 236	Day 1653	Days [1632, 1673]
	Week 242	Day 1695	Days [1674, 1715]
	Week 248	Day 1737	Days [1716, 1757]
	Week 254	Day 1779	Days [1758, 1799]
	Week 260	Day 1821	Days [1800, 1841]

For early termination visit (ETV), the window of last derived visit before ETV will end at one day before ETV

[a] Relative to the infusion day (day 1)

[b] Visit day is calculated by (visit date – date of infusion date + 1) if post infusion and (visit date – date of infusion date) if before infusion

[c] Baseline visit value is defined as the last available measurement prior to dosing.

[d] FVIII activity assay values within 72-hour interval since last FVIII use are excluded prior to windowing derivation.

[e] PCR collection to occur until at least 3 consecutive negative results are obtained. Subjects who have not had 3 consecutive negative samples by Week 52 should continue to have PCR testing every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

[f] Urine test starts with week 4, 8, 12, 16, the corresponding windows are Days [2, 42], Days [43, 70], Days [71, 98], Days [99, 126], respectively.

17.2 Preferred terms suggestive of thromboembolic events

confusional state (10010305)
muscular weakness (10028372)
swelling (100426740)
peripheral swelling-10030124)
odema Peripheral (10048959)
jaundice (10023126)
urine output decreased (10059895)
pain in extremity (10033425)
erythema (10015150)
dyspnea (10013968)
chest pain (10008479)
chest discomfort (10008469)
tachycardia (10043071)
haemoptysis (10018964)
presyncope (10026653)
headache (10019211)
hypoaesthesia (10020937)
eye pain (10015958)
eye swelling (10015967)
visual impairment (10047571)
visual acuity reduced (10047531)