Official Title: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

NCT Number: NCT04323098

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 20 April 2023

STATISTICAL ANALYSIS PLAN FOR ONE-YEAR ANALYSIS

(1-Year Analysis SAP)

Protocol Number:	270-303
Study Title:	A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Version:	1.0
Date:	21 FEB 2023

Approvals

Statistical Analysis Plan

Title: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

Protocol: 270-303, Amendment 2, 25 MAY 2021

Date: 21 FEB 2023

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1 SAP SYNOPSIS

TITLE OF STUDY: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

PROTOCOL NUMBER: 270-303

STUDY OBJECTIVES AND DESIGN

Study 270-303 is a Phase 3b, single-arm, open-label study designed to assess whether BMN 270 at a dose of 6E13 vg/kg with prophylactic corticosteroids, can safely and effectively improve the FVIII activity profiles and alter the clinical phenotype of hemophilia A (HA) patients with residual FVIII activity ≤ 1 IU/dL.

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy in the efficacy evaluation period (for subjects receiving prior FVIII prophylaxis, from Week 5 post-BMN 270 infusion [Study Day 33] or the end of FVIII prophylaxis plus the washout period [3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life], whichever is later, to subject's last visit up to the data cutoff for the 1-year analysis, hereafter referred to as "Post-FVIII prophylaxis period")

  Note: All enrolled subjects received FVIII prophylaxis and no subject was on emicizumab prophylaxis prior to BMN 270 infusion in this study

- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes irrespective of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 following intravenous infusion of BMN 270

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

Approximately 20 adult subjects with severe HA (22 actual) enrolled at approximately 15 sites (10 sites actual) worldwide will receive BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. In order to ensure sufficient baseline data to enable evaluation of BMN 270's impact on FVIII use and bleeding rate, subjects must have high-quality, well-documented historical data available concerning previous bleeding episodes and exogenous FVIII usage over the previous 12 months in order to be eligible to enroll in the study.

The primary analysis of the study will be performed after all subjects have been followed for at least 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52). After the primary analysis (1-Year Analysis), long-term safety and efficacy will continue to be assessed in all subjects for a total of approximately 5 years.

ANALYSIS POPULATIONS

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 by the time of the data cutoff.

Prophylactic corticosteroids completers are the subjects who received > 90% of the completed the protocol-specified 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion (i.e., the subjects who were on or above the recommended corticosteroid dose by the study protocol for >= 120 days in the first 19 weeks post BMN 270 infusion).

The ITT population will be the primary analysis population for efficacy and safety evaluations. Unless otherwise specified, all data will be summarized and presented side-by-side for the two analysis populations for comparison purposes.

When applicable, additional sensitivity analyses may be carried out for the Per-Protocol (PP) analysis population, defined as a subset of the ITT population 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 prior to database snapshot/lock and documented in the clinical study report (CSR).

STUDY ENDPOINTS AND ANALYSES:

FVIII activity, annualized FVIII utilization and annualized number of bleeding episodes

The primary efficacy endpoint is:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) post-BMN 270 infusion

Each subject's FVIII activity level at Week 52 is defined as the median of the values obtained within the analysis window at Weeks 49-52 as defined in Appendix 20.1. The baseline value will be imputed as 1 IU/dL, since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion. Post-BMN 270 infusion values for FVIII activity will be excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy.

The primary analysis of the change from baseline to Week 52 in FVIII activity will be a one-sample t-test on the ITT population. Missing values at Week 52 will be imputed using the imputation methods specified in Section 13.2.1. Supportive and sensitivity analyses of the primary efficacy endpoint are described in Section 13.2.2.

The first three secondary efficacy endpoints are:

- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes irrespective of exogenous FVIII replacement treatment (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) in the efficacy evaluation period ("Post-FVIII prophylaxis period")

The changes from baseline in ABR and annualized FVIII utilization will be tested using Wilcoxon signed-rank tests (primary method) and one-sample t-tests (supportive method). Other supportive and sensitivity analyses are specified in Section 13.3.1.

Patient-reported outcomes

The following patient-reported outcomes (PROs) will be used to assess subject quality of life (QoL) during the study:

- Change from baseline in the total score of HAEMO-QoL-A at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the EQ-5D-5L score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 of the study post-BMN 270 infusion

The QoL endpoints including the sub-scale/sub-domain scores (except for PROBE) will be summarized descriptively for the ITT population using the observed cases by visit up to the data cutoff. The p-value and 95% CI for the change from baseline based on two-sided t-test will be provided for descriptive purposes. PROBE will be analyzed externally through a separate statistical analysis plan.

Safety evaluations

Analyses of safety endpoints will be descriptive based on the ITT population. Adverse events (AEs), AEs assessed by the investigator as related to BMN 270, corticosteroid use or non-steroidal immunosuppressant use, serious adverse events (SAEs), SAEs assessed by the investigator as related to BMN 270, corticosteroid use or non-steroidal immunosuppressant use, AEs leading to study discontinuation, deaths, and events of special interest (EOSI) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). AEs and AEs assessed by the investigator as related to BMN 270 will also be summarized by severity. Exposure-adjusted summaries will also be provided.

Clinical laboratory tests will be summarized descriptively. Shift tables tabulating Common Terminology Criteria for Adverse Events (CTCAE) grade at baseline vs worst post-baseline grade will be provided.

2 TABLE OF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV5	Adeno-associated virus Type 5
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FVIII	Coagulation factor VIII
GGT	Gamma-glutamyl transferase
HA	Hemophilia A
hFVIII	Human coagulation factor VIII
HLT	High Level Term
ICH	International Conference on Harmonisation
IP	Investigational product
ITT	Intention-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LT	Liver test
LLoQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures

NAb	Neutralizing antibody
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PBMC	Peripheral blood mononuclear cells
PP	Per-protocol
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SFU	Spot forming units
SMQ	Standardized MedDRA query
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction inhibition
vg	Vector genomes
WHO	World Health Organization

4 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be implemented in the analysis of 1-year data collected under clinical study protocol 270-303 (Amendment 2, 25 MAY 2021), "A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients". This SAP (1-Year Analysis SAP) contains definitions of analysis populations, derived variables, and statistical methods for the evaluations of efficacy and safety of BMN 270.

4.1 Study Overview and Objectives

Study 270-303 is a Phase 3b, single-arm, open-label study designed to assess whether BMN 270 at a dose of 6E13 vg/kg with prophylactic corticosteroids, can safely and effectively improve the FVIII activity profiles and alter the clinical phenotype of hemophilia A (HA) patients with residual FVIII activity ≤ 1 IU/dL.

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy in the efficacy evaluation period (for subjects receiving prior FVIII prophylaxis, from Week 5 post-BMN 270 infusion [Study Day 33] or the end of FVIII prophylaxis plus the washout period [3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life], whichever is later, to subject's last visit up to the data cutoff for the 1-year analysis, hereafter referred to as "Post-FVIII prophylaxis period")
- Note: All enrolled subjects received FVIII prophylaxis and no subject was on emicizumab prophylaxis prior to BMN 270 infusion in this study
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes irrespective of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")

- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 following intravenous infusion of BMN 270

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

4.2 Study Design

Approximately 20 adult subjects with severe HA (22 actual) enrolled at approximately 15 sites (10 sites actual) worldwide will receive BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. In order to ensure sufficient baseline data to enable evaluation of BMN 270's impact on FVIII use and bleeding rate, subjects must have high-quality, well-documented historical data available concerning previous bleeding episodes and exogenous FVIII usage over the previous 12 months in order to be eligible to enroll in the study.

An interim analysis on non-efficacy data was performed in March 2022 after 10 treated subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26) (data cutoff date: 20 DEC 2021), to support the regulatory application of BMN 270 for the treatment of HA. The pre-specified analysis of non-efficacy data at the interim analysis was described in the 270-303 Interim Statistical Analysis Plan (dated 28 JAN 2022). Additional interim analysis of selected efficacy endpoints (e.g., FVIII activity level) may be conducted to support regulatory agency's ongoing review of BMN 270 marketing applications.

To minimize potential bias in performing statistical analysis during ongoing study and to assure safe and ethical conduct of the clinical trial, an independent Data Monitoring Committee (DMC), consisting of experts in clinical trials, statistics, and hemophilia, will be convened. The DMC has sole access during the trial to amalgamated FVIII activity levels, FVIII and emicizumab usage, and bleeding data, and reviews available safety and efficacy (e.g., FVIII activity) data during the study on an ongoing basis.

The primary analysis of the study will be performed after all subjects have been followed for at least 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52). After the primary analysis (1-Year Analysis), long-term safety and efficacy will continue to be assessed in all subjects for a total of approximately 5 years.

4.3 Study Population

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

- Males ≥ 18 years of age with HA and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history, at the time of signing the informed consent
- Must have been on prophylactic hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available

Subjects with detectable pre-existing antibodies to the adeno-associated virus Type 5 (AAV5) capsid are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies with titer level below the minimum required dilution (< 20). None of the enrolled subjects had detectable pre-existing AAV5 capsid antibodies in this study.

Refer to the study protocol for a complete list of all inclusion and exclusion criteria.

4.4 Study Dosage and Administration

Each subject will receive a single intravenous (IV) infusion of BMN 270 at 6E13 vg/kg. The volume of infusion will depend on the subject's weight.

4.5 Sample Size Determination

Approximately 20 subjects (22 actual) were planned to be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects with an AAV5 antibody titer that is detectable but below the minimum required dilution (< 20) at Screening. For the primary efficacy endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in human FVIII (hFVIII) activity at Week 52 (during Weeks 49 - 52) from baseline (baseline value imputed to be 1 IU/dL) is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the one-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05).

4.6 Randomization Methods and Blinding

Study 270-303 is a single-arm open-label study. No randomization or blinding will be performed. The process of data analysis and communication of analysis results will be specified in the Study 270-303 Data Dissemination Plan.

5 GENERAL ANALYSIS CONSIDERATIONS

Safety and efficacy variables will be summarized descriptively. Descriptive statistics include subject count, mean, median, standard deviation, 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. 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 collected at various time points within a subject. Figures may be provided to visualize distribution or trend of data. Subgroup analyses may be performed, if appropriate.

5.1 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 by the time of the data cutoff.

Prophylactic corticosteroids completers are the subjects who received > 90% of the protocol-specified 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion (i.e., the subjects who were on or above the recommended corticosteroid dose by the study protocol for >= 120 days in the first 19 weeks post BMN 270 infusion [Day 1 to Day 133]).

The ITT population will be the primary analysis population for efficacy and safety evaluations. Unless otherwise specified, all data will be summarized and presented side-by-side for the two analysis populations for comparison purposes.

When applicable, additional sensitivity analyses may be carried out for the Per-Protocol (PP) analysis population, defined as a subset of the ITT population 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 prior to database snapshot/lock and documented in the clinical study report (CSR).

5.2 Treatment Group Presentation

In general, if more than one dose level is used in the study, statistical summaries for each endpoint will be presented by BMN 270 dose levels subjects were assigned to and overall. Otherwise, all subjects will be summarized in one group.

5.3 Study Day Derivation

Study day is assigned as follows:

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

5.4 Visit Windows for Analysis

All efficacy and safety data will be summarized by week or by a duration of multiple weeks based on windows defined by study days, wherever applicable. An assessment for a subject will be classified according to the study day of the assessment and its corresponding analysis visit window (see Appendix 20.1 Analysis Visit Windows).

For the primary, secondary, and other efficacy endpoints, windows of multiple weeks are defined based on ranges of study days. Median, mean assessments, or annualized values from these windows may be used in efficacy analyses as deemed appropriate (see Section 13).

For the tertiary efficacy endpoints and the safety endpoints such as liver function tests and vital signs, the windows are designated for each scheduled week of visit and centered on a target day; for example, the target day for a Week 4 visit is Study Day 29. 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.

Appendix 20.1 Analysis Visit Windows lists the weeks assigned for the analyses of the clinical endpoint assessments and the corresponding range of treatment days (window) during which a visit may have occurred by analysis parameter.

5.5 Baseline Value

The baseline values of the annualized utilization of exogenous FVIII replacement therapy and the annualized number of bleeding episodes are calculated using the12-month historical data prior to 270-303 study screening up until the BMN 270 infusion date.

An imputed baseline FVIII activity of 1 IU/dL will be used for the change from baseline analysis since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion.

The baseline values of other assessments are defined as the last available measurement prior to the administration of BMN 270 unless otherwise specified.

5.6 Handling of Dropouts and Missing Data

If a subject withdraws from the study prematurely, the subject will be asked to complete an Early Termination Visit (ETV), the data from which will be included in summaries and analyses.

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 when possible and the duration is the longest possible duration.

FVIII activity levels below the lower limit of quantitation (LLoQ) will be imputed as 0 IU/dL. To reduce variation caused by random fluctuation, FVIII activity will be analyzed as the median of observed values within each analysis visit window as defined in Appendix 20.1. Missing FVIII activity values will be imputed as follows.

- Dropout missing:
  For subjects who discontinue from the study early, missing FVIII activity values post-discontinuation will be imputed to be 0 IU/dL through the data cutoff date for the analysis.
- Intermittent missing:
  For subjects who continue the study, missing FVIII activity values (e.g., due to a missed study visit) will be imputed to be the smaller of the last prior non-missing value and the next non-missing value. In rare cases where the next value is unavailable for a subject who did not drop out, the missing value will be imputed through linear extrapolation using the last two prior non-missing values, capped at the last non-missing value.

Other missing data imputation for the primary efficacy endpoint and the secondary efficacy endpoints are specified in the corresponding analysis sections.

Other missing data will not be imputed unless otherwise stated.

6 SUBJECT DISPOSITION

The number of subjects screened, number and percentage of screen failures by screen failure reasons will be summarized for all subjects screened. Subjects are considered enrolled into the study if the Baseline visit was completed, and the enrollment date is defined as the Baseline visit date. The number of subjects enrolled and the number and percentage by reason for subjects enrolled but not treated will be provided. Inclusion in and exclusion from analysis populations, as well as reason for exclusion, will be summarized for all subjects enrolled.

7 DISCONTINUATION AND COMPLETION

For treated subjects who prematurely discontinue study participation prior to the Week 52 visit or during the long-term follow-up period, the primary reason for discontinuation will be summarized for the ITT population. The number and percentage of subjects who are continuing the study at the data cutoff date for the 1-year analysis and subjects who completed Week 52 visit will also be provided for all treated subjects.

8 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. A data listing of protocol deviations will be provided as well.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be summarized include

- age at enrollment (years)
- age group (>= 18 - < 65, >= 65)
- 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 (years)
    - type of treatment for hemophilia A (FVIII prophylaxis or emicizumab)
    - history of FVIII inhibitor (Yes/No)
    - FVIII genotyping results
    - number of target joints
    - body location of target joints
    - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL) including values within 72 hours after a FVIII infusion
- baseline FVIII activity (IU/dL) excluding values within 72 hours after a FVIII infusion
- 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 annualized bleeding rate (ABR) (treated bleeds/year)
- baseline ABR (all bleeds/year)

10 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).

11 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 (IP) and within 30 days prior to Screening
- Concomitant medication - any medication taken after the initiation of the IP

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

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), and by NIH hepatotoxicity likelihood grades and preferred name as well. 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 corticosteroid course, duration per corticosteroid course, and number of corticosteroid courses will be summarized for therapeutic purposes. Compliance to protocol-specified 19-week prophylactic corticosteroid regimen will be summarized (e.g., the number and proportion of subjects who received protocol-recommended dose of prophylactic corticosteroids for > 90% of time in the first 19 weeks post BMN 270 infusion). Non-steroidal immunosuppressants may be summarized as well.

Baseline FVIII prophylaxis treatment will be summarized by type (extended half-life, standard half-life, or plasma derived) and drug preferred name.

12 EXTENT OF EXPOSURE TO STUDY DRUG

Each subject will receive a single intravenous infusion of BMN 270, and the volume of infusion will depend on the subject's weight. Actual dose (vg/kg), duration of infusion, initial and overall rate of infusion for each subject will be summarized descriptively. Investigational product dosing compliance will be assessed by providing descriptive summaries of actual dose, number and percentage of subjects with administered IP infusions below the planned dose, subjects with dose changes, and various reasons of dose changes. The post-BMN 270 follow-up time of each subject will be summarized descriptively.

A data listing of drug exposure will be provided.

13 EFFICACY EVALUATIONS

This section describes the analyses to be undertaken for the primary, secondary, and other efficacy variables as described in the protocol.

13.1 Efficacy Evaluation Periods

To avoid breakthrough bleeding, subjects only discontinued exogenous prophylactic FVIII replacement therapy after 4 weeks following infusion of BMN 270. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on earlier results.

For the primary data analysis, the efficacy evaluation period for

- Efficacy endpoints such as ABR (all bleeds and treated bleeds), number of bleeds (all bleeds and treated bleeds), annualized FVIII utilization, annualized FVIII infusions and PROs: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), whichever is later, until subjects complete the study, reach the last visit by data cutoff for the analysis, or withdraw from the study (ETV), whichever is the earliest
-
- Efficacy endpoint of FVIII activity based on chromogenic substrate assay: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) until subjects complete the study, reach the last visit by data cutoff for the analysis, withdraw from the study (ETV) (FVIII activities post withdrawal will be imputed to be 0 IU/dL through the data cutoff date for the analysis), or resume routine FVIII prophylaxis (should that occur) (restart of FVIII prophylaxis is defined as the first usual FVIII prophylaxis administered at least once a week for ≥ 4 consecutive weeks), whichever is the earliest
- Efficacy endpoint of FVIII activity based on one-stage assay: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) until subjects complete the study, reach the last visit by data cutoff for the analysis, resume routine FVIII prophylaxis or start emicizumab prophylaxis (should that occur) (start of emicizumab prophylaxis is defined as the first emicizumab injection among 2 or more emicizumab injections administered within 31 days), whichever is the earliest.

For supportive data analyses, the efficacy evaluation period for

- Efficacy endpoint of FVIII activity: will be defined as from BMN 270 infusion to until subjects complete the study, reach the last visit by data cutoff for the analysis, or withdraw from the study (ETV), whichever is the earliest

- Efficacy endpoints such as ABR, number of treated bleeds, annualized FVIII utilization, annualized FVIII infusions: will be some of the efficacy evaluation periods listed in Table 13.1.1. In addition, descriptive summary will be provided in Weeks 1-4 and Week 1-end of FVIII prophylaxis (defined as end of week 4 post-BMN 270 infusion or end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life, whichever is later)

Time to discontinuation of FVIII prophylaxis post-BMN 270 infusion and duration of efficacy evaluation period for primary analysis of the aforementioned efficacy endpoints will be summarized.

Table 13.1.1: Efficacy Evaluation Periods for the Analyses of Number of Bleeding Episodes, FVIII Utilization and FVIII Infusions

Efficacy Evaluation Period	Start Point	End Point	Analysis
Post-FVIII prophylaxis period	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff	Primary, Wilcoxon signed-rank test
Post-FVIII prophylaxis – week 52	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff or end of Week 52 post-BMN 270 infusion, whichever is earlier	Supportive, Wilcoxon signed-rank test
Post-FVIII prophylaxis – restart of prophylactic treatment up to Week 52	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff, end of Week 52 post-BMN 270 infusion or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, Wilcoxon signed-rank test
Post-FVIII prophylaxis – restart of prophylactic treatment up to last visit	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, Wilcoxon signed-rank test

Note: end of FVIII prophylaxis is defined as last usual FVIII prophylaxis not followed by another usual FVIII prophylaxis for at least 28 days.

Restart of prophylactic treatment means restart of FVIII or start emicizumab prophylaxis. Restart of FVIII prophylaxis is defined as the first usual FVIII prophylaxis administered at least once a week for ≥ 4 consecutive weeks. Start of emicizumab prophylaxis is defined as the first emicizumab injection among 2 or more emicizumab injections administered within 31 days.

13.2 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) post-BMN 270 infusion

Each subject's FVIII activity level at Week 52 is defined as the median of the values obtained within the analysis window at Weeks 49-52 as defined in Appendix 20.1. The baseline value will be imputed as 1 IU/dL, since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion. Post-BMN 270 infusion values for FVIII activity will be excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy.

The change from baseline in the FVIII activity at Week 52 post-BMN 270 infusion will be tested using a one-sample t-test. The hypotheses are:

H_0 (null hypothesis): Change = 0 versus H_1 (alternative hypothesis): Change $\neq$ 0.

Only positive changes indicate efficacy.

13.2.1 Primary Analysis for the Primary Efficacy Endpoint

The primary analysis of FVIII activity will be based on the ITT population. If any subject in the ITT population has no assessment available at Week 52, the imputation methods specified in Section 5.6 will be used to impute the missing value. Specifically, if the subject discontinues from the study prior to Week 52, the missing value will be imputed to be 0 IU/dL at Week 52; if the subject continues the study, the missing value will be imputed to be the smaller of the median value in the subject's last 4-week window prior to Week 52 containing a valid observation and the median value in the subject's next 4-week window post Week 52 containing a valid observation. If the value of the next 4-week window is unavailable (e.g., Week 52 is the last visit by the data cutoff date), the missing value will be imputed through linear extrapolation using the median values in last two 4-week windows prior to Week 52 containing a valid observation, capped at the value in the last 4-week window.

A listing of subjects with no assessment available at Week 52 will be provided, including the imputed value and associated analysis visit window as well as the next available FVIII activity value after Week 52 and associated analysis visit window, if available. This is to assess potential bias in missing data imputation.

13.2.2 Supportive and Sensitivity Analyses for the Primary Efficacy Endpoint

The FVIII activity level will be summarized descriptively in 4-week or 6-week analysis visit windows with missing data imputed from baseline up to the last possible visit by the data cutoff for the 1-year analysis. The visits and analysis visit windows are defined in Appendix 20.1 Analysis Visit Windows. Each subject's FVIII activity level in an analysis visit window is defined as the median of the values obtained within the window. The number and proportion of subjects achieving FVIII activity level per chromogenic assay of < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - <15 IU/dL, between the levels of >= 15 -< 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will also be summarized every 4 or 6 weeks post-BMN 270 infusion up to data cutoff. The number and proportion of subjects whose FVIII activity is < 5, >= 5 - < 40 and >= 40 IU/dL will also be provided.

Boxplots of median FVIII activity values using chromogenic substrate assay by 4-week or 6-week windows (Appendix 20.1 Analysis Visit Windows) over time will be provided.

The 4-week or 6-week analysis will be repeated using efficacy evaluation period for supportive analysis of FVIII activity without imputation for the ITT population.

The maximum of each subject's FVIII activity levels (medians of the values in analysis visit windows defined in Appendix 20.1), and the time to the maximum level, will be summarized descriptively. The number and proportion of subjects whose maximum FVIII activity level is < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - < 15 IU/dL, between the levels of >= 15 - < 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will also be summarized.

The primary and supportive analyses described above may be conducted for FVIII activity levels measured by one-stage clotting assay.

To investigate the relationship between the FVIII activity values by one-stage clotting and chromogenic substrate assays, a linear regression to fit a line to the observed values by these two assays will be conducted for the ITT population.

The FVIII activity levels and their changes from baseline will be summarized descriptively at milestone timepoints defined as the end of every 6 months post-BMN 270 infusion (e.g., Week 26, Week 52 with the analysis visit windows defined in Appendix 20.1). Missing data will be imputed using the imputation methods specified in Section 5.6. In addition, proportion of subjects whose FVIII level is < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - < 15 IU/dL, between the levels of >= 15 - < 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will be

summarized. The change in FVIII activity between certain milestone timepoints (e.g., between Week 26 and Week 52) and between Week 52 and the maximal FVIII activity by Week 52 will also be summarized.

Exploratory analyses including univariate and multiple logistic regression may be performed to evaluate associations between demographic and baseline characteristics and other parameters and FVIII activity at Week 52 to assess potential predictors of variability.

One-sample t-test on the change from baseline in the FVIII activity at Week 52 using observed cases (i.e., no missing data imputation) will be performed as sensitivity analyses.

The primary analysis for the change from baseline in FVIII activity at Week 52 will be conducted for the PP population when applicable.

To investigate the robustness of the primary analysis, which uses the median FVIII activity value if more than one assessment falls within an analysis window, a sensitivity analysis may be performed using the mean of the multiple assessments. This sensitivity analysis will be based on the ITT population with the same imputation method as the primary analysis.

A mixed model for repeated measures (MMRM) approach may be used with the observed cases for the ITT population to evaluate the impact of missing data assuming missing at random. The model will include visit (every 4 weeks, from baseline to Week 52) as the only factor and will use an unstructured covariance matrix. The least squares (LS) mean change from baseline to Week 52 will be reported.

13.3 Secondary and Tertiary Efficacy Endpoints

13.3.1 Annualized Bleeding Rate and FVIII Utilization

The first three secondary efficacy endpoints are:

- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes irrespective of exogenous FVIII replacement treatment (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) in the efficacy evaluation period ("Post-FVIII prophylaxis period")

The annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy is defined as

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

The annualized number of bleeding episodes (for all bleeds and treated bleeds), i.e., annualized bleeding rate (ABR for all bleeds and treated bleeds), is defined as

$$\frac{\text{Number of bleeding episodes (all bleeds or treated bleeds) during the calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

The calculation period in the above formulas for the post-baseline value is:

- For the primary analyses, the efficacy evaluation period "Post-FVIII prophylaxis period" as defined in Section 13.1.
- For the supportive analyses, other efficacy evaluation periods as defined in Section 13.1.

If a post-baseline value is missing, e.g., when a subject drops out before Week 5, the change in ABR and annualized FVIII utilization will be imputed as the median value of the changes of all subjects' observed cases.

The baseline values of ABR and FVIII utilization for each subject will be derived based on the 12-month historical data prior to BMN 270 infusion.

For the number of bleeding episodes, only treated bleeds will be considered. Bleeds due to surgery/procedure are not included. Only treatments that were recorded as "treatment for bleed" are included in the determination of a treated bleed. The definition of a "treated bleed" is as follows:

- If a bleed is directly followed by a hemophilia medication reported to be a "treatment for bleed" within 72 hours (or 3 calendar days if time is not available), it is considered to be a treated bleed. This bleed and the first treatment thereafter are referred to as a pair
- If multiple bleeds of different type or/and different anatomical location occur within 24 hours (of the last bleed before treatment for bleed) or on the same calendar day, the subsequent treatment within 72 hours (or 3 calendar days if time is not available) is considered to pair with each of these bleeds. Each of these bleeds that is within 72 hours (or 3 calendar days if time is not available) of the subsequent treatment is therefore considered to be a treated bleed

- Two bleeds of the same type and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours (or 3 calendar days if time is not available) 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 regardless whether the second bleed is followed by a treatment

The changes from baseline in ABR and annualized FVIII utilization will be tested using Wilcoxon signed-rank tests (primary method) and one-sample t-tests (supportive method). Only negative changes indicate efficacy.

Supportive and sensitivity analyses on ABR (for all bleeds and treated bleeds) and annualized FVIII utilization will include:

The number of bleeding episodes and total FVIII utilization will be listed by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1). The ABR and annualized FVIII utilization (IU/kg/year) will be summarized descriptively by periods.

The changes from baseline in ABR (for all bleeds and treated bleeds) and annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will also be analyzed using data in different efficacy evaluation periods as defined in Table 13.1.1.

The ABR may be analyzed using a generalized linear mixed model assuming negative binomial as the underlying distribution. The model will include period (pre-BMN 270 infusion [baseline period], Week 1-end of FVIII Prophylaxis, Post FVIII Prophylaxis-Last Visit) as the only factor. The analysis will be performed using the SAS GENMOD procedure where the duration of each period is included as an OFFSET to account for varying follow-up times and a REPEATED statement is included to account for the intra-patient comparison.

The primary analyses on ABR and FVIII utilization may be conducted for the PP population when applicable.

13.3.2 Haemo-QoL-A and Other Patient-Reported Outcomes

The following patient-reported outcomes (PROs) will be used to assess subjects' quality of life (QoL) during the study:

- Change from baseline in the total score of HAEMO-QoL-A at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the EQ-5D-5L score at Week 52 of the study post-BMN 270 infusion

- Change from baseline in the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 of the study post-BMN 270 infusion

The PROs will be assessed at baseline, Week 4, Week 12, Week 26, Week 52 and every 6 months starting with Week 76 per protocol-scheduled assessments.

The QoL endpoints including the sub-scale/sub-domain scores (except for PROBE) will be summarized descriptively for the ITT population using the observed cases by visit up to the data cutoff. The p-value and 95% CI for the change from baseline based on two-sided t-test will be provided for descriptive purposes. PROBE will be analyzed externally through a separate statistical analysis plan.

13.4 Other Efficacy Endpoints

13.4.1 FVIII Infusions

Total and annualized number of FVIII infusions will be listed by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1), and the annualized FVIII infusion rates will be summarized descriptively by periods.

The same analysis of FVIII utilization (IU/kg) and number of FVIII infusions will be performed for the following types of FVIII infusion in the primary efficacy evaluation period:

- Treatment for bleed
- Surgery/procedure
- Usual prophylaxis (routine)
- One-time prophylaxis

Analysis based on the type of FVIII product used will be performed if applicable.

13.4.2 Bleeds

The following types of bleeds will be analyzed:

- Treated joint bleeding episodes
- Treated target joint bleeding episodes (bleeding episodes that occur at joints which are listed as target joints at study entry)
- Treated spontaneous bleeding episodes

- Treated traumatic bleeding episodes

The analyses include tabulation of total and annualized counts by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1), and descriptive summary of the corresponding annualized rates. Target joint resolution with the incidence and percentage of the resolved target joints post BMN-270 treatment will be assessed.

13.5 Examination of Efficacy by Subgroups

Subgroup analyses will be performed on the efficacy endpoints including FVIII activity by chromogenic assay, annualized FVIII utilization (IU/kg/year) and ABR (for all bleeds and treated bleeds) based on the following baseline characteristics:

- Age at enrollment: >= 18 - < 30 years vs. >= 30 - < 50 years vs. >= 50 years old
- Target joint at baseline: Yes vs. No

Subgroup analyses based on other baseline characteristics may also be performed for exploratory purposes if the sample size permits.

14 SAFETY EVALUATIONS

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

14.1 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 or worsened in severity following initiation of study drug administration. Adverse events will be coded in accordance with 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 IP-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 electronic case report form (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 the protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of hemophilia, and whether or not they require 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 following 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.

The following types of AEs will be summarized: all AEs, AEs assessed by investigator as related to BMN 270, SAEs, SAEs assessed by investigator as related to BMN 270, AEs leading to study discontinuation, deaths, and events of special interest (EOSI), AEs associated with corticosteroid use or non-steroidal immunosuppressant use, and AEs reported as laboratory abnormalities with clinical significance. Listings will be provided.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 5.6 will be applied.

14.1.1 All Adverse Events

The incidence and number of events for all TEAEs will be summarized by SOC, PT and severity. Exposure-adjusted summaries, in which each subject's incidence is divided by the duration of follow-up, will also be provided. 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 a TEAE listing, a listing of AEs reported under Investigations SOC will also be provided.

14.1.2 Drug-Related Adverse Events

All TEAEs assessed by investigator as study drug related (i.e., ADRs) will be summarized by SOC, PT and severity.

14.1.3 Deaths and Serious Adverse Events

Serious adverse events and SAEs assessed by investigator as study drug related (i.e., serious ADRs) will be summarized by SOC, PT and severity. Listings of deaths and all SAEs will be provided.

14.1.4 Adverse Events Causing Early Discontinuation

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

14.1.5 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
  - Alanine transaminase (ALT) elevation (Preferred term: "Alanine aminotransferase increased").
  - AEs related to liver function, defined using the MedDRA search strategy high level term (HLT = "Liver function analyses").
  - Potential Hy's law cases
    - ALT or aspartate transaminase (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, infusion-associated reaction, Hypersensitivity, Anaphylactic or Anaphylactic reactions
  - Infusion-related reactions, defined as AEs occurring during BMN 270 infusion or within 6 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
  - Infusion-associated reactions, defined as AEs occurring within 48 hours post-infusion
  - 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 activity > 170 IU/dL (based on chromogenic assay) 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 IU/dL. (The preferred terms are listed in Appendix 20.2.)

- Development of anti-FVIII neutralizing antibodies (NAb) as measured by Nijmegen modified Bethesda Assay (Preferred term: "Anti factor VIII antibody positive")
- Any new diagnosis of malignancy (except non-melanoma skin cancer)

14.1.6 Adverse Events Related to immunosuppressant therapy

Adverse events that are related to corticosteroid or non-steroidal immunosuppressant will be summarized by SOC, PT and severity. In addition, a list of subjects with the AEs related to immunosuppressant therapy will be provided.

14.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, hematology, urine tests, and coagulation. Clinical laboratory test values and change from Baseline will be summarized descriptively by visit. 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. The same analyses based on mean or median ALT values will be conducted. ALT values and change from Baseline over time will be summarized descriptively. Summaries of ALT elevations including baseline ALT, time from infusion to ALT > ULN, ALT > 3x ULN, ALT > 5x ULN, ALT > 1.5x baseline value or > ULN, , peak ALT level, and duration of ALT elevation will be provided. Local ALT assessments will be analyzed similarly as the central ALT assessments, if needed. Similar analyses will be applied to other liver tests including AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, and alkaline phosphatase (ALP), if needed.

In addition, incidences 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.

14.3 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.

14.4 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.

14.5 Viral Shedding

Viral shedding will be extensively studied at protocol specified time points including Baseline, BMN 270 infusion day, and post BMN 270 infusion until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at these time points. Testing of semen will continue at least 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 semen samples by Week 52 should continue to have PCR testing in semen 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).

The vector genomes tested in extracted body samples will be summarized by visit with descriptive statistics and in 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 lower limit of quantitation (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.

15 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 and 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 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 and 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 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. Test results will be summarized and data listings will be generated reporting positive or negative and the number of SFU 10^6 PBMC for each peptide pool and control 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.

16 CLINICAL PHARMACOLOGY

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

17 OTHER ANALYSIS

Study 270-303 was ongoing during the COVID-19 pandemic and remained ongoing despite the disruption that occurred. The study began enrollment after the pandemic was declared but had no impact on study sample size. However, pandemic might affect the study conduct.

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID-19 pandemic on the study conduct and results, especially for the treatment effect as estimated in the trial. Summaries of study participation with missing visits, study disposition and protocol deviations due to COVID-19 pandemic will be provided.

18 REFERENCES

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19 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	21FEB2023		Initial version

20 APPENDICES

20.1 Analysis Visit Windows

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
FVIII activity assays	Baseline[c]	Day -7 – Day -1	≤ Day 1
	Weeks 1 - 4		Days [2, 32]
	Weeks 5 - 8		Days [33, 60]
	Weeks 9 - 12		Days [61, 88]
	Weeks 13 - 16		Days [89, 116]
	Weeks 17 - 20		Days [117, 144]
	Weeks 21 - 24		Days [145, 172]
	Weeks 23 – 26		Days [159, 186]
	Weeks 25 - 28		Days [173, 200]
	Weeks 29 - 32		Days [201, 228]
	Weeks 33 - 36		Days [229, 256]
	Weeks 37 - 40		Days [257, 284]
	Weeks 41 - 44		Days [285, 312]
	Weeks 45 - 48		Days [313, 340]
	Weeks 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/EY	Day 729	Days [715, 743]
	Week 110	Day 771	Days [744, 792]
	Week 116	Day 813	Days [793, 834]
	Week 122	Day 855	Days [835, 876]
	Week 128	Day 897	Days [877, 918]
	Week 134	Day 939	Days [919, 960]
	Week 140	Day 981	Days [961, 1002]
	Week 146	Day 1023	Days [1003, 1044]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 152	Day 1065	Days [1045, 1078]
	Week 156/EY	Day 1093	Days [1079, 1114]
	Week 162	Day 1135	Days [1115, 1156]
	Week 168	Day 1177	Days [1157, 1198]
	Week 174	Day 1219	Days [1199, 1240]
	Week 180	Day 1261	Days [1241, 1282]
	Week 186	Day 1303	Days [1283, 1324]
	Week 192	Day 1345	Days [1325, 1366]
	Week 198	Day 1387	Days [1367, 1408]
	Week 204	Day 1429	Days [1409, 1442]
	Week 208/EY	Day 1457	Days [1443, 1478]
	Week 214	Day 1499	Days [1479, 1520]
	Week 220	Day 1541	Days [1521, 1562]
	Week 226	Day 1583	Days [1563, 1604]
	Week 232	Day 1625	Days [1605, 1646]
	Week 238	Day 1667	Days [1647, 1688]
	Week 244	Day 1709	Days [1689, 1730]
	Week 250	Day 1751	Days [1731, 1772]
	Week 256	Day 1793	Days [1773, 1806]
	Week 260/EY	Day 1821	Days [1807, 1835]
Note: median or mean of the assessments within the above windows will be used for analysis.			
Annualized utilization (IU/kg) of exogenous FVIII replacement therapy, ABR	Baseline[d]		< Day 1
	Week 1 – FVIII Prophylaxis End		Days [1, the later date of Day 32 or the end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life]
	Post FVIII Prophylaxis–Week 52		Days [the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), 368]
	Post FVIII Prophylaxis Period		≥ the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life)

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
Note: all assessments within the above defined windows will be used to derive the corresponding endpoint.			
Number of FVIII infusions, Bleeds	Baseline[d]		< Day 1
	Week 1 – FVIII Prophylaxis End		Days [1, the later date of Day 32 or the end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life]
	Post FVIII Prophylaxis–Week 52		Days [the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), 368]
	Post FVIII Prophylaxis Period		≥ the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life)
Note: all assessments within the above defined windows will be used in analysis.			
PROs	Baseline[c]	Day -7 to Day -1	≤ Day 5
	Week 4	Day 29	Days [6, 57]
	Week 12	Day 85	Days [58, 134]
	Week 26	Day 183	Days [135, 274]
	Week 52	Day 365	Days [275, 448]
	Week 76	Day 533	Days [449, 630]
	Week 104/EY	Day 730	Days [631, 812]
	Week 128	Day 897	Days [813, 994]
	Week 156/EY	Day 1096	Days [995, 1176]
	Week 180	Day 1261	Days [1177, 1358]
	Week 208/EY	Day 1461	Days [1359, 1540]
	Week 232	Day 1625	Days [1541, 1722]
	Week 260/EY	Day 1826	Days [1723, 1840]
PBMC (ELISpot)	Baseline[c]	Day -7 to Day -1	≤ Day 1
	Week 2	Day 15	Days [2, 22]
	Week 4	Day 29	Days [23, 36]
	Week 6	Day 43	Days [37, 40]
	Week 8	Day 57	Days [41, 64]
	Week 10	Day 71	Days [65, 78]
	Week 12	Day 85	Days [79, 92]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 14	Day 99	Days [93, 106]
	Week 16	Day 113	Days [107, 120]
	Week 18	Day 127	Days [121, 134]
	Week 20	Day 141	Days [135, 148]
	Week 22	Day 155	Days [149, 162]
	Week 24	Day 169	Days [163, 176]
	Week 26	Day 183	Days [177, 190]
	Week 28	Day 197	Days [191, 204]
	Week 30	Day 211	Days [205, 218]
	Week 32	Day 225	Days [219, 232]
	Week 34	Day 239	Days [233, 246]
	Week 36	Day 253	Days [247, 281]
	Week 44	Day 309	Days [282, 337]
	Week 52	Day 365	Days [338, 393]
	Week 64	Day 449	Days [408, 491]
	Week 76	Day 533	Days [492, 575]
	Week 88	Day 617	Days [576, 659]
	Week 100	Day 701	Days [660, 715]
	Week 104/EY	Day 730	Days [716, 772]
	Week 116	Day 814	Days [773, 856]
	Week 128	Day 898	Days [857, 940]
	Week 140	Day 982	Days [941, 1024]
	Week 152	Day 1066	Days [1025, 1080]
	Week 156/EY	Day 1096	Days [1081, 1138]
	Week 168	Day 1180	Days [1139, 1222]
	Week 180	Day 1264	Days [1223, 1306]
	Week 192	Day 1348	Days [1307, 1390]
	Week 204	Day 1432	Days [1391, 1446]
	Week 208/EY	Day 1461	Days [1447, 1503]
	Week 220	Day 1545	Days [1504, 1587]
	Week 232	Day 1629	Days [1588, 1671]
	Week 244	Day 1713	Days [1672, 1755]
	Week 256	Day 1797	Days [1756, 1811]
	Week 260/EY	Day 1826	Days [1812, 1840]
Liver tests, Vital signs, and other central lab tests	Baseline[c]	Day -1	≤ Day 1
	Week 1	Day 8	Days [2, 11]
	Week 2	Day 15	Days [12, 18]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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/EY	Day 730	Days [715, 743]
	Week 110	Day 772	Days [744, 792]
	Week 116	Day 814	Days [793, 835]
	Week 122	Day 856	Days [836, 877]
	Week 128	Day 898	Days [878, 919]
	Week 134	Day 940	Days [920, 961]
	Week 140	Day 982	Days [962, 1003]
	Week 146	Day 1024	Days [1004, 1045]
	Week 152	Day 1066	Days [1046, 1079]
	Week 156/EY	Day 1096	Days [1080, 1117]
	Week 162	Day 1138	Days [1118, 1159]
	Week 168	Day 1180	Days [1160, 1201]
	Week 174	Day 1222	Days [1202, 1243]
	Week 180	Day 1264	Days [1244, 1285]
	Week 186	Day 1306	Days [1286, 1327]
	Week 192	Day 1348	Days [1328, 1369]
	Week 198	Day 1390	Days [1370, 1411]
	Week 204	Day 1432	Days [1412, 1446]
	Week 208/EY	Day 1461	Days [1447, 1482]
	Week 214	Day 1503	Days [1483, 1524]
	Week 220	Day 1545	Days [1525, 1566]
	Week 226	Day 1587	Days [1567, 1608]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 232	Day 1629	Days [1609, 1650]
	Week 238	Day 1671	Days [1651, 1692]
	Week 244	Day 1713	Days [1693, 1734]
	Week 250	Day 1755	Days [1735, 1776]
	Week 256	Day 1797	Days [1777, 1811]
	Week 260/EY	Day 1826	Days [1812, 1840]

[a] Relative to the BMN 270 infusion day (Day 1)

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

[c] Baseline visit value of FVIII activity is defined as the last available measurement prior to BMN 270 infusion excluding those within 72 hours after a FVIII infusion. Baseline visit value of other assessments is defined as the last available measurement prior to BMN 270 infusion.

[d] Baseline value is derived from the period between 12 months prior to 270-303 screening and the BMN 270 infusion day.

EY: end of year visit.

20.2 Preferred Terms Suggestive of Thromboembolic Events

confusional state (10010305)
muscular weakness (10028372)
swelling (10042674)
peripheral swelling(10048959)
odema Peripheral (10030124)
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 (10036653)
headache (10019211)
hypoaesthesia (10020937)
eye pain (10015958)
eye swelling (10015967)
visual impairment (10047571)
visual acuity reduced (10047531)

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Every: Approval Task	PI PI
Every: Approval Task	PI tative PI

STATISTICAL ANALYSIS PLAN FOR ONE-YEAR ANALYSIS

(1-Year Analysis SAP)

Protocol Number: 270-303

Study Title: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

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

Version: 2.0

Date: 20 APR 2023

Approvals

Statistical Analysis Plan

Title: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

Protocol: 270-303, Amendment 2, 25 MAY 2021

Date: 20 APR 2023

Approvals

_____	___/___/___	_____	___/___/___
PI , PhD PI , Statistical Science, Biostatistician	DD MM YY	PI , MB BS, PhD PI Head of Late-Stage Clinical Development	DD MM YY
_____	___/___/___	_____	___/___/___
PI PI , Data Analytics Science Statistical Programmer	DD MM YY	PI , MD, PhD PI Clinical Sciences	DD MM YY
_____	___/___/___	_____	___/___/___
PI , PhD PI , Statistical Science Head of Statistical Science	DD MM YY	PI , MD PI Pharmacovigilance	DD MM YY

{See Appended Electronic Signature Pages}

1 SAP SYNOPSIS

TITLE OF STUDY: A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

PROTOCOL NUMBER: 270-303

STUDY OBJECTIVES AND DESIGN

Study 270-303 is a Phase 3b, single-arm, open-label study designed to assess whether BMN 270 at a dose of 6E13 vg/kg with prophylactic corticosteroids, can safely and effectively improve the FVIII activity profiles and alter the clinical phenotype of hemophilia A (HA) patients with residual FVIII activity ≤ 1 IU/dL.

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy in the efficacy evaluation period (for subjects receiving prior FVIII prophylaxis, from Week 5 post-BMN 270 infusion [Study Day 33] or the end of FVIII prophylaxis plus the washout period [3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life], whichever is later, to subject's last visit up to the data cutoff for the 1-year analysis, hereafter referred to as "Post-FVIII prophylaxis period")

  Note: All enrolled subjects received FVIII prophylaxis and no subject was on emicizumab prophylaxis prior to BMN 270 infusion in this study

- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes irrespective of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 following intravenous infusion of BMN 270

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

Approximately 20 adult subjects with severe HA (22 actual) enrolled at approximately 15 sites (10 sites actual) worldwide will receive BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. In order to ensure sufficient baseline data to enable evaluation of BMN 270's impact on FVIII use and bleeding rate, subjects must have high-quality, well-documented historical data available concerning previous bleeding episodes and exogenous FVIII usage over the previous 12 months in order to be eligible to enroll in the study.

The primary analysis of the study will be performed after all subjects have been followed for at least 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52). After the primary analysis (1-Year Analysis), long-term safety and efficacy will continue to be assessed in all subjects for a total of approximately 5 years.

ANALYSIS POPULATIONS

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 by the time of the data cutoff.

The modified intention-to-treat (mITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 and were on adequate prophylactic hemophilia therapy for at least 12 months (>= 52 doses of FVIII replacement therapy in 12 months if on FVIII prophylaxis) prior to BMN 270 infusion.

Prophylactic corticosteroids completers are the subjects who received > 90% of the completed the protocol-specified 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion (i.e., the subjects who were on or above the recommended corticosteroid dose by the study protocol for >= 120 days in the first 19 weeks post BMN 270 infusion).

The mITT population will be the primary analysis population for efficacy evaluations, and the ITT population will be used for the primary safety analysis. Unless otherwise specified, all data will be summarized and presented side-by-side for the three analysis populations for comparison purposes.

When applicable, additional sensitivity analyses may be carried out for the Per-Protocol (PP) analysis population, defined as a subset of the ITT population 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 prior to database snapshot/lock and documented in the clinical study report (CSR).

STUDY ENDPOINTS AND ANALYSES:

FVIII activity, annualized FVIII utilization and annualized number of bleeding episodes

The primary efficacy endpoint is:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) post-BMN 270 infusion

Each subject's FVIII activity level at Week 52 is defined as the median of the values obtained within the analysis window at Weeks 49-52 as defined in Appendix 20.1. The baseline value will be imputed as 1 IU/dL, since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion. Post-BMN 270 infusion values for FVIII activity will be excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy.

The primary analysis of the change from baseline to Week 52 in FVIII activity will be a one-sample t-test on the mITT population. Missing values at Week 52 will be imputed using the imputation methods specified in Section 13.2.1. Supportive and sensitivity analyses of the primary efficacy endpoint are described in Section 13.2.2.

The first three secondary efficacy endpoints are:

- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes irrespective of exogenous FVIII replacement treatment (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) in the efficacy evaluation period ("Post-FVIII prophylaxis period")

The changes from baseline in ABR and annualized FVIII utilization will be tested using Wilcoxon signed-rank tests (primary method) and one-sample t-tests (supportive method). Other supportive and sensitivity analyses are specified in Section 13.3.1.

Patient-reported outcomes

The following patient-reported outcomes (PROs) will be used to assess subject quality of life (QoL) during the study:

- Change from baseline in the total score of HAEMO-QoL-A at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the EQ-5D-5L score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 of the study post-BMN 270 infusion

The QoL endpoints including the sub-scale/sub-domain scores (except for PROBE) will be summarized descriptively for the mITT population using the observed cases by visit up to the data cutoff. The p-value and 95% CI for the change from baseline based on two-sided t-test will be provided for descriptive purposes. PROBE will be analyzed externally through a separate statistical analysis plan.

Safety evaluations

Analyses of safety endpoints will be descriptive based on the ITT population. Adverse events (AEs), AEs assessed by the investigator as related to BMN 270, corticosteroid use or non-steroidal immunosuppressant use, serious adverse events (SAEs), SAEs assessed by the investigator as related to BMN 270, corticosteroid use or non-steroidal immunosuppressant use, AEs leading to study discontinuation, deaths, and events of special interest (EOSI) will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). AEs and AEs assessed by the investigator as related to BMN 270 will also be summarized by severity. Exposure-adjusted summaries will also be provided.

Clinical laboratory tests will be summarized descriptively. Shift tables tabulating Common Terminology Criteria for Adverse Events (CTCAE) grade at baseline vs worst post-baseline grade will be provided.

2 TABLE OF CONTENTS

LIST OF TABLES

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV5	Adeno-associated virus Type 5
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOSI	Events of special interest
ETV	Early termination visit
FVIII	Coagulation factor VIII
GGT	Gamma-glutamyl transferase
HA	Hemophilia A
hFVIII	Human coagulation factor VIII
HLT	High Level Term
ICH	International Conference on Harmonisation
IP	Investigational product
ITT	Intention-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LT	Liver test
LLoQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat

MMRM	Mixed model for repeated measures
NAb	Neutralizing antibody
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PBMC	Peripheral blood mononuclear cells
PP	Per-protocol
PRO	Patient-reported outcome
PT	Preferred term
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SFU	Spot forming units
SMQ	Standardized MedDRA query
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction inhibition
vg	Vector genomes
WHO	World Health Organization

4 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be implemented in the analysis of 1-year data collected under clinical study protocol 270-303 (Amendment 2, 25 MAY 2021), "A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients". This SAP (1-Year Analysis SAP) contains definitions of analysis populations, derived variables, and statistical methods for the evaluations of efficacy and safety of BMN 270.

4.1 Study Overview and Objectives

Study 270-303 is a Phase 3b, single-arm, open-label study designed to assess whether BMN 270 at a dose of 6E13 vg/kg with prophylactic corticosteroids, can safely and effectively improve the FVIII activity profiles and alter the clinical phenotype of hemophilia A (HA) patients with residual FVIII activity ≤ 1 IU/dL.

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy in the efficacy evaluation period (for subjects receiving prior FVIII prophylaxis, from Week 5 post-BMN 270 infusion [Study Day 33] or the end of FVIII prophylaxis plus the washout period [3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life], whichever is later, to subject's last visit up to the data cutoff for the 1-year analysis, hereafter referred to as "Post-FVIII prophylaxis period")
- Note: All enrolled subjects received FVIII prophylaxis and no subject was on emicizumab prophylaxis prior to BMN 270 infusion in this study
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes irrespective of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")

- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 following intravenous infusion of BMN 270

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

4.2 Study Design

Approximately 20 adult subjects with severe HA (22 actual) enrolled at approximately 15 sites (10 sites actual) worldwide will receive BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. In order to ensure sufficient baseline data to enable evaluation of BMN 270's impact on FVIII use and bleeding rate, subjects must have high-quality, well-documented historical data available concerning previous bleeding episodes and exogenous FVIII usage over the previous 12 months in order to be eligible to enroll in the study.

An interim analysis on non-efficacy data was performed in March 2022 after 10 treated subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26) (data cutoff date: 20 DEC 2021), to support the regulatory application of BMN 270 for the treatment of HA. The pre-specified analysis of non-efficacy data at the interim analysis was described in the 270-303 Interim Statistical Analysis Plan (dated 28 JAN 2022). Additional interim analysis of selected efficacy endpoints (e.g., FVIII activity level) may be conducted to support regulatory agency's ongoing review of BMN 270 marketing applications.

To minimize potential bias in performing statistical analysis during ongoing study and to assure safe and ethical conduct of the clinical trial, an independent Data Monitoring Committee (DMC), consisting of experts in clinical trials, statistics, and hemophilia, will be convened. The DMC has sole access during the trial to amalgamated FVIII activity levels, FVIII and emicizumab usage, and bleeding data, and reviews available safety and efficacy (e.g., FVIII activity) data during the study on an ongoing basis.

The primary analysis of the study will be performed after all subjects have been followed for at least 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52). After the primary analysis (1-Year Analysis), long-term safety and efficacy will continue to be assessed in all subjects for a total of approximately 5 years.

4.3 Study Population

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

- Males ≥ 18 years of age with HA and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history, at the time of signing the informed consent
- Must have been on prophylactic hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available

Subjects with detectable pre-existing antibodies to the adeno-associated virus Type 5 (AAV5) capsid are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies with titer level below the minimum required dilution (< 20). None of the enrolled subjects had detectable pre-existing AAV5 capsid antibodies in this study.

Refer to the study protocol for a complete list of all inclusion and exclusion criteria.

4.4 Study Dosage and Administration

Each subject will receive a single intravenous (IV) infusion of BMN 270 at 6E13 vg/kg. The volume of infusion will depend on the subject's weight.

4.5 Sample Size Determination

Approximately 20 subjects (22 actual) were planned to be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects with an AAV5 antibody titer that is detectable but below the minimum required dilution (< 20) at Screening. For the primary efficacy endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in human FVIII (hFVIII) activity at Week 52 (during Weeks 49 - 52) from baseline (baseline value imputed to be 1 IU/dL) is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the one-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05).

4.6 Randomization Methods and Blinding

Study 270-303 is a single-arm open-label study. No randomization or blinding will be performed. The process of data analysis and communication of analysis results will be specified in the Study 270-303 Data Dissemination Plan.

5 GENERAL ANALYSIS CONSIDERATIONS

Safety and efficacy variables will be summarized descriptively. Descriptive statistics include subject count, mean, median, standard deviation, 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. 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 collected at various time points within a subject. Figures may be provided to visualize distribution or trend of data. Subgroup analyses may be performed, if appropriate.

5.1 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 by the time of the data cutoff.

The modified intention-to-treat (mITT) population is defined as all subjects who received BMN 270 infusion in the Study 270-303 and were on adequate prophylactic hemophilia therapy for at least 12 months (>= 52 doses of FVIII replacement therapy in 12 months if on FVIII prophylaxis) prior to BMN 270 infusion.

Prophylactic corticosteroids completers are the subjects who received > 90% of the protocol-specified 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion (i.e., the subjects who were on or above the recommended corticosteroid dose by the study protocol for >= 120 days in the first 19 weeks post BMN 270 infusion [Day 1 to Day 133]).

The mITT population will be the primary analysis population for efficacy evaluations, and the ITT population will be used for the primary safety analysis. Unless otherwise specified, all data will be summarized and presented side-by-side for the three analysis populations for comparison purposes.

When applicable, additional sensitivity analyses may be carried out for the Per-Protocol (PP) analysis population, defined as a subset of the ITT population 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 prior to database snapshot/lock and documented in the clinical study report (CSR).

5.2 Treatment Group Presentation

In general, if more than one dose level is used in the study, statistical summaries for each endpoint will be presented by BMN 270 dose levels subjects were assigned to and overall. Otherwise, all subjects will be summarized in one group.

5.3 Study Day Derivation

Study day is assigned as follows:

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

5.4 Visit Windows for Analysis

All efficacy and safety data will be summarized by week or by a duration of multiple weeks based on windows defined by study days, wherever applicable. An assessment for a subject will be classified according to the study day of the assessment and its corresponding analysis visit window (see Appendix 20.1 Analysis Visit Windows).

For the primary, secondary, and other efficacy endpoints, windows of multiple weeks are defined based on ranges of study days. Median, mean assessments, or annualized values from these windows may be used in efficacy analyses as deemed appropriate (see Section 13).

For the tertiary efficacy endpoints and the safety endpoints such as liver function tests and vital signs, the windows are designated for each scheduled week of visit and centered on a target day; for example, the target day for a Week 4 visit is Study Day 29. 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.

Appendix 20.1 Analysis Visit Windows lists the weeks assigned for the analyses of the clinical endpoint assessments and the corresponding range of treatment days (window) during which a visit may have occurred by analysis parameter.

5.5 Baseline Value

The baseline values of the annualized utilization of exogenous FVIII replacement therapy and the annualized number of bleeding episodes are calculated using the12-month historical data prior to 270-303 study screening up until the BMN 270 infusion date.

An imputed baseline FVIII activity of 1 IU/dL will be used for the change from baseline analysis since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion.

The baseline values of other assessments are defined as the last available measurement prior to the administration of BMN 270 unless otherwise specified.

5.6 Handling of Dropouts and Missing Data

If a subject withdraws from the study prematurely, the subject will be asked to complete an Early Termination Visit (ETV), the data from which will be included in summaries and analyses.

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 when possible and the duration is the longest possible duration.

FVIII activity levels below the lower limit of quantitation (LLoQ) will be imputed as 0 IU/dL. To reduce variation caused by random fluctuation, FVIII activity will be analyzed as the median of observed values within each analysis visit window as defined in Appendix 20.1. Missing FVIII activity values will be imputed as follows.

- Dropout missing:
  For subjects who discontinue from the study early, missing FVIII activity values post-discontinuation will be imputed to be 0 IU/dL through the data cutoff date for the analysis.
- Intermittent missing:
  For subjects who continue the study, missing FVIII activity values (e.g., due to a missed study visit) will be imputed to be the smaller of the last prior non-missing value and the next non-missing value. In rare cases where the next value is unavailable for a subject who did not drop out, the missing value will be imputed through linear extrapolation using the last two prior non-missing values, capped at the last non-missing value.

Other missing data imputation for the primary efficacy endpoint and the secondary efficacy endpoints are specified in the corresponding analysis sections.

Other missing data will not be imputed unless otherwise stated.

6 SUBJECT DISPOSITION

The number of subjects screened, number and percentage of screen failures by screen failure reasons will be summarized for all subjects screened. Subjects are considered enrolled into the study if the Baseline visit was completed, and the enrollment date is defined as the Baseline visit date. The number of subjects enrolled and the number and percentage by reason for subjects enrolled but not treated will be provided. Inclusion in and exclusion from analysis populations, as well as reason for exclusion, will be summarized for all subjects enrolled.

7 DISCONTINUATION AND COMPLETION

For treated subjects who prematurely discontinue study participation prior to the Week 52 visit or during the long-term follow-up period, the primary reason for discontinuation will be summarized for the ITT population. The number and percentage of subjects who are continuing the study at the data cutoff date for the 1-year analysis and subjects who completed Week 52 visit will also be provided for all treated subjects.

8 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. A data listing of protocol deviations will be provided as well.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject demographic and baseline characteristics to be summarized include

- age at enrollment (years)
- age group (>= 18 - < 65, >= 65)
- 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 (years)
    - type of treatment for hemophilia A (FVIII prophylaxis or emicizumab)
    - history of FVIII inhibitor (Yes/No)
    - FVIII genotyping results
    - number of target joints
    - body location of target joints
    - ambulatory assist device requirement (Yes/No)
- baseline FVIII activity (IU/dL) including values within 72 hours after a FVIII infusion
- baseline FVIII activity (IU/dL) excluding values within 72 hours after a FVIII infusion
- 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 annualized bleeding rate (ABR) (treated bleeds/year)
- baseline ABR (all bleeds/year)

10 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).

11 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 (IP) and within 30 days prior to Screening
- Concomitant medication - any medication taken after the initiation of the IP

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

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), and by NIH hepatotoxicity likelihood grades and preferred name as well. 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 corticosteroid course, duration per corticosteroid course, and number of corticosteroid courses will be summarized for therapeutic purposes. Compliance to protocol-specified 19-week prophylactic corticosteroid regimen will be summarized (e.g., the number and proportion of subjects who received protocol-recommended dose of prophylactic corticosteroids for > 90% of time in the first 19 weeks post BMN 270 infusion). Non-steroidal immunosuppressants may be summarized as well.

Baseline FVIII prophylaxis treatment will be summarized by type (extended half-life, standard half-life, or plasma derived) and drug preferred name.

12 EXTENT OF EXPOSURE TO STUDY DRUG

Each subject will receive a single intravenous infusion of BMN 270, and the volume of infusion will depend on the subject's weight. Actual dose (vg/kg), duration of infusion, initial and overall rate of infusion for each subject will be summarized descriptively. Investigational product dosing compliance will be assessed by providing descriptive summaries of actual dose, number and percentage of subjects with administered IP infusions below the planned dose, subjects with dose changes, and various reasons of dose changes. The post-BMN 270 follow-up time of each subject will be summarized descriptively.

A data listing of drug exposure will be provided.

13 EFFICACY EVALUATIONS

This section describes the analyses to be undertaken for the primary, secondary, and other efficacy variables as described in the protocol.

13.1 Efficacy Evaluation Periods

To avoid breakthrough bleeding, subjects only discontinued exogenous prophylactic FVIII replacement therapy after 4 weeks following infusion of BMN 270. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on earlier results.

For the primary data analysis, the efficacy evaluation period for

- Efficacy endpoints such as ABR (all bleeds and treated bleeds), number of bleeds (all bleeds and treated bleeds), annualized FVIII utilization, annualized FVIII infusions and PROs: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), whichever is later, until subjects complete the study, reach the last visit by data cutoff for the analysis, or withdraw from the study (ETV), whichever is the earliest
- Efficacy endpoint of FVIII activity based on chromogenic substrate assay: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) until subjects complete the study, reach the last visit by data cutoff for the analysis, withdraw from the study (ETV) (FVIII activities post withdrawal will be imputed to be 0 IU/dL through the data cutoff date for the analysis), or resume routine FVIII prophylaxis (should that occur) (restart of FVIII prophylaxis is defined as the first usual FVIII prophylaxis administered at least once a week for ≥ 4 consecutive weeks), whichever is the earliest
- Efficacy endpoint of FVIII activity based on one-stage assay: will be defined as starting from Week 5 post-BMN 270 infusion (Study Day 33) until subjects complete the study, reach the last visit by data cutoff for the analysis, resume routine FVIII prophylaxis or start emicizumab prophylaxis (should that occur) (start of emicizumab prophylaxis is defined as the first emicizumab injection among 2 or more emicizumab injections administered within 31 days), whichever is the earliest.

For supportive data analyses, the efficacy evaluation period for

- Efficacy endpoint of FVIII activity: will be defined as from BMN 270 infusion to until subjects complete the study, reach the last visit by data cutoff for the analysis, or withdraw from the study (ETV), whichever is the earliest

- Efficacy endpoints such as ABR, number of treated bleeds, annualized FVIII utilization, annualized FVIII infusions: will be some of the efficacy evaluation periods listed in Table 13.1.1. In addition, descriptive summary will be provided in Weeks 1-4 and Week 1-end of FVIII prophylaxis (defined as end of week 4 post-BMN 270 infusion or end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life, whichever is later)

Time to discontinuation of FVIII prophylaxis post-BMN 270 infusion and duration of efficacy evaluation period for primary analysis of the aforementioned efficacy endpoints will be summarized.

Table 13.1.1: Efficacy Evaluation Periods for the Analyses of Number of Bleeding Episodes, FVIII Utilization and FVIII Infusions

Efficacy Evaluation Period	Start Point	End Point	Analysis
Post-FVIII prophylaxis period	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff	Primary, Wilcoxon signed-rank test
Post-FVIII prophylaxis – week 52	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff or end of Week 52 post-BMN 270 infusion, whichever is earlier	Supportive, Wilcoxon signed-rank test
Post-FVIII prophylaxis – restart of prophylactic treatment up to Week 52	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff, end of Week 52 post-BMN 270 infusion or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, Wilcoxon signed-rank test
Post-FVIII prophylaxis – restart of prophylactic treatment up to last visit	Start of Week 5 post-BMN 270 infusion or end of FVIII prophylaxis plus 3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life, whichever is later	Last visit by data cutoff or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, Wilcoxon signed-rank test

Note: end of FVIII prophylaxis is defined as last usual FVIII prophylaxis not followed by another usual FVIII prophylaxis for at least 28 days.

Restart of prophylactic treatment means restart of FVIII or start emicizumab prophylaxis. Restart of FVIII prophylaxis is defined as the first usual FVIII prophylaxis administered at least once a week for ≥ 4 consecutive weeks. Start of emicizumab prophylaxis is defined as the first emicizumab injection among 2 or more emicizumab injections administered within 31 days.

13.2 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Week 52 (during Weeks 49 - 52) post-BMN 270 infusion

Each subject's FVIII activity level at Week 52 is defined as the median of the values obtained within the analysis window at Weeks 49-52 as defined in Appendix 20.1. The baseline value will be imputed as 1 IU/dL, since there will be no washout of severe hemophilia A subjects' usual FVIII prophylaxis (in order to avoid increasing the risk of bleeding) prior to BMN 270 infusion. Post-BMN 270 infusion values for FVIII activity will be excluded from analysis if obtained within 72 hours (or 3 calendar days if time is not available) since the last infusion of exogenous FVIII replacement therapy.

The change from baseline in the FVIII activity at Week 52 post-BMN 270 infusion will be tested using a one-sample t-test. The hypotheses are:

H_0 (null hypothesis): Change = 0 versus H_1 (alternative hypothesis): Change $\neq$ 0.

Only positive changes indicate efficacy.

13.2.1 Primary Analysis for the Primary Efficacy Endpoint

The primary analysis of FVIII activity will be based on the mITT population. If any subject in the mITT population has no assessment available at Week 52, the imputation methods specified in Section 5.6 will be used to impute the missing value. Specifically, if the subject discontinues from the study prior to Week 52, the missing value will be imputed to be 0 IU/dL at Week 52; if the subject continues the study, the missing value will be imputed to be the smaller of the median value in the subject's last 4-week window prior to Week 52 containing a valid observation and the median value in the subject's next 4-week window post Week 52 containing a valid observation. If the value of the next 4-week window is unavailable (e.g., Week 52 is the last visit by the data cutoff date), the missing value will be imputed through linear extrapolation using the median values in last two 4-week windows prior to Week 52 containing a valid observation, capped at the value in the last 4-week window.

A listing of subjects with no assessment available at Week 52 will be provided, including the imputed value and associated analysis visit window as well as the next available FVIII activity value after Week 52 and associated analysis visit window, if available. This is to assess potential bias in missing data imputation.

13.2.2 Supportive and Sensitivity Analyses for the Primary Efficacy Endpoint

The FVIII activity level will be summarized descriptively in 4-week or 6-week analysis visit windows with missing data imputed from baseline up to the last possible visit by the data cutoff for the 1-year analysis. The visits and analysis visit windows are defined in Appendix 20.1 Analysis Visit Windows. Each subject's FVIII activity level in an analysis visit window is defined as the median of the values obtained within the window. The number and proportion of subjects achieving FVIII activity level per chromogenic assay of < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - <15 IU/dL, between the levels of >= 15 -< 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will also be summarized every 4 or 6 weeks post-BMN 270 infusion up to data cutoff. The number and proportion of subjects whose FVIII activity is < 5, >= 5 - < 40 and >= 40 IU/dL will also be provided.

Boxplots of median FVIII activity values using chromogenic substrate assay by 4-week or 6-week windows (Appendix 20.1 Analysis Visit Windows) over time will be provided.

The 4-week or 6-week analysis will be repeated using efficacy evaluation period for supportive analysis of FVIII activity without imputation for the mITT population.

The maximum of each subject's FVIII activity levels (medians of the values in analysis visit windows defined in Appendix 20.1), and the time to the maximum level, will be summarized descriptively. The number and proportion of subjects whose maximum FVIII activity level is < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - < 15 IU/dL, between the levels of >= 15 - < 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will also be summarized.

The primary and supportive analyses described above may be conducted for FVIII activity levels measured by one-stage clotting assay.

To investigate the relationship between the FVIII activity values by one-stage clotting and chromogenic substrate assays, a linear regression to fit a line to the observed values by these two assays will be conducted for the mITT population.

The FVIII activity levels and their changes from baseline will be summarized descriptively at milestone timepoints defined as the end of every 6 months post-BMN 270 infusion (e.g., Week 26, Week 52 with the analysis visit windows defined in Appendix 20.1). Missing data will be imputed using the imputation methods specified in Section 5.6. In addition, proportion of subjects whose FVIII level is < LLoQ (3 IU/dL), between levels of >= LLoQ (3 IU/dL) - < 5 IU/dL, between the levels of >= 5 - < 15 IU/dL, between the levels of >= 15 - < 40 IU/dL, between the levels of >= 40 - <= 150 IU/dL, and > 150 IU/dL will be

summarized. The change in FVIII activity between certain milestone timepoints (e.g., between Week 26 and Week 52) and between Week 52 and the maximal FVIII activity by Week 52 will also be summarized.

Exploratory analyses including univariate and multiple logistic regression may be performed to evaluate associations between demographic and baseline characteristics and other parameters and FVIII activity at Week 52 to assess potential predictors of variability.

One-sample t-test on the change from baseline in the FVIII activity at Week 52 using observed cases (i.e., no missing data imputation) will be performed as sensitivity analyses.

The primary analysis for the change from baseline in FVIII activity at Week 52 will be conducted for the PP population when applicable.

To investigate the robustness of the primary analysis, which uses the median FVIII activity value if more than one assessment falls within an analysis window, a sensitivity analysis may be performed using the mean of the multiple assessments. This sensitivity analysis will be based on the mITT population with the same imputation method as the primary analysis.

A mixed model for repeated measures (MMRM) approach may be used with the observed cases for the mITT population to evaluate the impact of missing data assuming missing at random. The model will include visit (every 4 weeks, from baseline to Week 52) as the only factor and will use an unstructured covariance matrix. The least squares (LS) mean change from baseline to Week 52 will be reported.

13.3 Secondary and Tertiary Efficacy Endpoints

13.3.1 Annualized Bleeding Rate and FVIII Utilization

The first three secondary efficacy endpoints are:

- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes irrespective of exogenous FVIII replacement treatment (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post-FVIII prophylaxis period")
- The change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) in the efficacy evaluation period ("Post-FVIII prophylaxis period")

The annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy is defined as

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

The annualized number of bleeding episodes (for all bleeds and treated bleeds), i.e., annualized bleeding rate (ABR for all bleeds and treated bleeds), is defined as

$$\frac{\text{Number of bleeding episodes (all bleeds or treated bleeds) during the calculation period}}{\text{Total number of days during the calculation period}} \times 365.25$$

The calculation period in the above formulas for the post-baseline value is:

- For the primary analyses, the efficacy evaluation period "Post-FVIII prophylaxis period" as defined in Section 13.1.
- For the supportive analyses, other efficacy evaluation periods as defined in Section 13.1.

If a post-baseline value is missing, e.g., when a subject drops out before Week 5, the change in ABR and annualized FVIII utilization will be imputed as the median value of the changes of all subjects' observed cases.

The baseline values of ABR and FVIII utilization for each subject will be derived based on the 12-month historical data prior to 270-303 study screening up until the BMN 270 infusion date.

For the number of bleeding episodes, only treated bleeds will be considered. Bleeds due to surgery/procedure are not included. Only treatments that were recorded as "treatment for bleed" are included in the determination of a treated bleed. The definition of a "treated bleed" is as follows:

- If a bleed is directly followed by a hemophilia medication reported to be a "treatment for bleed" within 72 hours (or 3 calendar days if time is not available), it is considered to be a treated bleed. This bleed and the first treatment thereafter are referred to as a pair
- If multiple bleeds of different type or/and different anatomical location occur within 24 hours (of the last bleed before treatment for bleed) or on the same calendar day, the subsequent treatment within 72 hours (or 3 calendar days if time is not available) is considered to pair with each of these bleeds. Each of these bleeds that is within 72 hours (or 3 calendar days if time is not available) of the subsequent treatment is therefore considered to be a treated bleed

- Two bleeds of the same type and at the same anatomical location are considered to be one bleed if the second occurs within 72 hours (or 3 calendar days if time is not available) 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 regardless whether the second bleed is followed by a treatment

The changes from baseline in ABR and annualized FVIII utilization will be tested using Wilcoxon signed-rank tests (primary method) and one-sample t-tests (supportive method). Only negative changes indicate efficacy.

Supportive and sensitivity analyses on ABR (for all bleeds and treated bleeds) and annualized FVIII utilization will include:

The number of bleeding episodes and total FVIII utilization will be listed by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1). The ABR and annualized FVIII utilization (IU/kg/year) will be summarized descriptively by periods.

The changes from baseline in ABR (for all bleeds and treated bleeds) and annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will also be analyzed using data in different efficacy evaluation periods as defined in Table 13.1.1.

The ABR may be analyzed using a generalized linear mixed model assuming negative binomial as the underlying distribution. The model will include period (pre-BMN 270 infusion [baseline period], Week 1-end of FVIII Prophylaxis, Post FVIII Prophylaxis-Last Visit) as the only factor. The analysis will be performed using the SAS GENMOD procedure where the duration of each period is included as an OFFSET to account for varying follow-up times and a REPEATED statement is included to account for the intra-patient comparison.

The primary analyses on ABR and FVIII utilization may be conducted for the PP population when applicable.

13.3.2 Haemo-QoL-A and Other Patient-Reported Outcomes

The following patient-reported outcomes (PROs) will be used to assess subjects' quality of life (QoL) during the study:

- Change from baseline in the total score of HAEMO-QoL-A at Week 52 of the study post-BMN 270 infusion
- Change from baseline in the EQ-5D-5L score at Week 52 of the study post-BMN 270 infusion

- Change from baseline in the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) score at Week 52 of the study post-BMN 270 infusion
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 of the study post-BMN 270 infusion

The PROs will be assessed at baseline, Week 4, Week 12, Week 26, Week 52 and every 6 months starting with Week 76 per protocol-scheduled assessments.

The QoL endpoints including the sub-scale/sub-domain scores (except for PROBE) will be summarized descriptively for the mITT population using the observed cases by visit up to the data cutoff. The p-value and 95% CI for the change from baseline based on two-sided t-test will be provided for descriptive purposes. PROBE will be analyzed externally through a separate statistical analysis plan.

13.4 Other Efficacy Endpoints

13.4.1 FVIII Infusions

Total and annualized number of FVIII infusions will be listed by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1), and the annualized FVIII infusion rates will be summarized descriptively by periods.

The same analysis of FVIII utilization (IU/kg) and number of FVIII infusions will be performed for the following types of FVIII infusion in the primary efficacy evaluation period:

- Treatment for bleed
- Surgery/procedure
- Usual prophylaxis (routine)
- One-time prophylaxis

Analysis based on the type of FVIII product used will be performed if applicable.

13.4.2 Bleeds

The following types of bleeds will be analyzed:

- Treated joint bleeding episodes
- Treated target joint bleeding episodes (bleeding episodes that occur at joints which are listed as target joints at study entry)
- Treated spontaneous bleeding episodes

- Treated traumatic bleeding episodes

The analyses include tabulation of total and annualized counts by subject and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, and the efficacy evaluation periods as defined in Table 13.1.1), and descriptive summary of the corresponding annualized rates. Target joint resolution with the incidence and percentage of the resolved target joints post BMN-270 treatment will be assessed.

13.5 Examination of Efficacy by Subgroups

Subgroup analyses will be performed on the efficacy endpoints including FVIII activity by chromogenic assay, annualized FVIII utilization (IU/kg/year) and ABR (for all bleeds and treated bleeds) based on the following baseline characteristics:

- Age at enrollment: >= 18 - < 30 years vs. >= 30 - < 50 years vs. >= 50 years old
- Target joint at baseline: Yes vs. No

Subgroup analyses based on other baseline characteristics may also be performed for exploratory purposes if the sample size permits.

14 SAFETY EVALUATIONS

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

14.1 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 or worsened in severity following initiation of study drug administration. Adverse events will be coded in accordance with 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 IP-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 electronic case report form (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 the protocol Section 10.2) should be reported as serious adverse events (whether or not they are bleeding events that are normal sequelae of hemophilia, and whether or not they require 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 following 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.

The following types of AEs will be summarized: all AEs, AEs assessed by investigator as related to BMN 270, SAEs, SAEs assessed by investigator as related to BMN 270, AEs leading to study discontinuation, deaths, and events of special interest (EOSI), AEs associated with corticosteroid use or non-steroidal immunosuppressant use, and AEs reported as laboratory abnormalities with clinical significance. Listings will be provided.

If the onset date or end date of an AE is partial, the same imputation rules described in Section 5.6 will be applied.

14.1.1 All Adverse Events

The incidence and number of events for all TEAEs will be summarized by SOC, PT and severity. Exposure-adjusted summaries, in which each subject's incidence is divided by the duration of follow-up, will also be provided. 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 a TEAE listing, a listing of AEs reported under Investigations SOC will also be provided.

14.1.2 Drug-Related Adverse Events

All TEAEs assessed by investigator as study drug related (i.e., ADRs) will be summarized by SOC, PT and severity.

14.1.3 Deaths and Serious Adverse Events

Serious adverse events and SAEs assessed by investigator as study drug related (i.e., serious ADRs) will be summarized by SOC, PT and severity. Listings of deaths and all SAEs will be provided.

14.1.4 Adverse Events Causing Early Discontinuation

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

14.1.5 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
  - Alanine transaminase (ALT) elevation (Preferred term: "Alanine aminotransferase increased").
  - AEs related to liver function, defined using the MedDRA search strategy high level term (HLT = "Liver function analyses").
  - Potential Hy's law cases
    - ALT or aspartate transaminase (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, infusion-associated reaction, Hypersensitivity, Anaphylactic or Anaphylactic reactions
  - Infusion-related reactions, defined as AEs occurring during BMN 270 infusion or within 6 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
  - Infusion-associated reactions, defined as AEs occurring within 48 hours post-infusion
  - 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 activity > 170 IU/dL (based on chromogenic assay) 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 IU/dL. (The preferred terms are listed in Appendix 20.2.)

- Development of anti-FVIII neutralizing antibodies (NAb) as measured by Nijmegen modified Bethesda Assay (Preferred term: "Anti factor VIII antibody positive")
- Any new diagnosis of malignancy (except non-melanoma skin cancer)

14.1.6 Adverse Events Related to immunosuppressant therapy

Adverse events that are related to corticosteroid or non-steroidal immunosuppressant will be summarized by SOC, PT and severity. In addition, a list of subjects with the AEs related to immunosuppressant therapy will be provided.

14.2 Clinical Laboratory Tests

Clinical laboratory tests include blood chemistry, hematology, urine tests, and coagulation. Clinical laboratory test values and change from Baseline will be summarized descriptively by visit. 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. The same analyses based on mean or median ALT values will be conducted. ALT values and change from Baseline over time will be summarized descriptively. Summaries of ALT elevations including baseline ALT, time from infusion to ALT > ULN, ALT > 3x ULN, ALT > 5x ULN, ALT > 1.5x baseline value or > ULN, , peak ALT level, and duration of ALT elevation will be provided. Local ALT assessments will be analyzed similarly as the central ALT assessments, if needed. Similar analyses will be applied to other liver tests including AST, gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, and alkaline phosphatase (ALP), if needed.

In addition, incidences 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.

14.3 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.

14.4 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.

14.5 Viral Shedding

Viral shedding will be extensively studied at protocol specified time points including Baseline, BMN 270 infusion day, and post BMN 270 infusion until at least 3 consecutive negative results are obtained. Body fluids including blood, saliva, semen, urine and stool will be tested by polymerase chain reaction (PCR) at these time points. Testing of semen will continue at least 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 semen samples by Week 52 should continue to have PCR testing in semen 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).

The vector genomes tested in extracted body samples will be summarized by visit with descriptive statistics and in 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 lower limit of quantitation (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.

15 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 and 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 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 and 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 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. Test results will be summarized and data listings will be generated reporting positive or negative and the number of SFU 10^6 PBMC for each peptide pool and control 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.

16 CLINICAL PHARMACOLOGY

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

17 OTHER ANALYSIS

Study 270-303 was ongoing during the COVID-19 pandemic and remained ongoing despite the disruption that occurred. The study began enrollment after the pandemic was declared but had no impact on study sample size. However, pandemic might affect the study conduct.

Additional analyses will be conducted as appropriate to evaluate the impact of the COVID-19 pandemic on the study conduct and results, especially for the treatment effect as estimated in the trial. Summaries of study participation with missing visits, study disposition and protocol deviations due to COVID-19 pandemic will be provided.

18 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.

US Food and Drug Administration. "Non-inferiority clinical trials to establish effectiveness. Guidance for industry." (2016).

19 SUMMARY OF CHANGES TO STUDY SAP

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	21FEB2023		Initial version
2.0	20APR2023	Section 5.1, Section 13	1. An mITT analysis population was defined to exclude subjects who were not on adequate prophylactic hemophilia therapy prior to BMN 270 infusion from the ITT population. The mITT population will be the primary analysis population for efficacy evaluations. 2. Clarification of baseline annualized utilization of exogenous FVIII replacement therapy and annualized number of bleeding episodes calculation time window.

20 APPENDICES

20.1 Analysis Visit Windows

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
FVIII activity assays	Baseline[c]	Day -7 – Day -1	≤ Day 1
	Weeks 1 - 4		Days [2, 32]
	Weeks 5 - 8		Days [33, 60]
	Weeks 9 - 12		Days [61, 88]
	Weeks 13 - 16		Days [89, 116]
	Weeks 17 - 20		Days [117, 144]
	Weeks 21 - 24		Days [145, 172]
	Weeks 23 – 26		Days [159, 186]
	Weeks 25 - 28		Days [173, 200]
	Weeks 29 - 32		Days [201, 228]
	Weeks 33 - 36		Days [229, 256]
	Weeks 37 - 40		Days [257, 284]
	Weeks 41 - 44		Days [285, 312]
	Weeks 45 - 48		Days [313, 340]
	Weeks 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/EY	Day 729	Days [715, 743]
	Week 110	Day 771	Days [744, 792]
	Week 116	Day 813	Days [793, 834]
	Week 122	Day 855	Days [835, 876]
	Week 128	Day 897	Days [877, 918]
	Week 134	Day 939	Days [919, 960]
	Week 140	Day 981	Days [961, 1002]
	Week 146	Day 1023	Days [1003, 1044]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 152	Day 1065	Days [1045, 1078]
	Week 156/EY	Day 1093	Days [1079, 1114]
	Week 162	Day 1135	Days [1115, 1156]
	Week 168	Day 1177	Days [1157, 1198]
	Week 174	Day 1219	Days [1199, 1240]
	Week 180	Day 1261	Days [1241, 1282]
	Week 186	Day 1303	Days [1283, 1324]
	Week 192	Day 1345	Days [1325, 1366]
	Week 198	Day 1387	Days [1367, 1408]
	Week 204	Day 1429	Days [1409, 1442]
	Week 208/EY	Day 1457	Days [1443, 1478]
	Week 214	Day 1499	Days [1479, 1520]
	Week 220	Day 1541	Days [1521, 1562]
	Week 226	Day 1583	Days [1563, 1604]
	Week 232	Day 1625	Days [1605, 1646]
	Week 238	Day 1667	Days [1647, 1688]
	Week 244	Day 1709	Days [1689, 1730]
	Week 250	Day 1751	Days [1731, 1772]
	Week 256	Day 1793	Days [1773, 1806]
	Week 260/EY	Day 1821	Days [1807, 1835]
Note: median or mean of the assessments within the above windows will be used for analysis.			
Annualized utilization (IU/kg) of exogenous FVIII replacement therapy, ABR	Baseline[d]		< Day 1
	Week 1 – FVIII Prophylaxis End		Days [1, the later date of Day 32 or the end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life]
	Post FVIII Prophylaxis–Week 52		Days [the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), 368]
	Post FVIII Prophylaxis Period		≥ the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life)

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
Note: all assessments within the above defined windows will be used to derive the corresponding endpoint.			
Number of FVIII infusions, Bleeds	Baseline[d]		< Day 1
	Week 1 – FVIII Prophylaxis End		Days [1, the later date of Day 32 or the end of FVIII prophylaxis plus 2 days for products of standard half-life or plasma-derived and 4 days for products of extended half-life]
	Post FVIII Prophylaxis–Week 52		Days [the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life), 368]
	Post FVIII Prophylaxis Period		≥ the later date of Day 33 or the end of FVIII prophylaxis plus the washout period (3 days for products of standard half-life or plasma-derived and 5 days for products of extended half-life)
Note: all assessments within the above defined windows will be used in analysis.			
PROs	Baseline[c]	Day -7 to Day -1	≤ Day 5
	Week 4	Day 29	Days [6, 57]
	Week 12	Day 85	Days [58, 134]
	Week 26	Day 183	Days [135, 274]
	Week 52	Day 365	Days [275, 448]
	Week 76	Day 533	Days [449, 630]
	Week 104/EY	Day 730	Days [631, 812]
	Week 128	Day 897	Days [813, 994]
	Week 156/EY	Day 1096	Days [995, 1176]
	Week 180	Day 1261	Days [1177, 1358]
	Week 208/EY	Day 1461	Days [1359, 1540]
	Week 232	Day 1625	Days [1541, 1722]
	Week 260/EY	Day 1826	Days [1723, 1840]
PBMC (ELISpot)	Baseline[c]	Day -7 to Day -1	≤ Day 1
	Week 2	Day 15	Days [2, 22]
	Week 4	Day 29	Days [23, 36]
	Week 6	Day 43	Days [37, 40]
	Week 8	Day 57	Days [41, 64]
	Week 10	Day 71	Days [65, 78]
	Week 12	Day 85	Days [79, 92]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 14	Day 99	Days [93, 106]
	Week 16	Day 113	Days [107, 120]
	Week 18	Day 127	Days [121, 134]
	Week 20	Day 141	Days [135, 148]
	Week 22	Day 155	Days [149, 162]
	Week 24	Day 169	Days [163, 176]
	Week 26	Day 183	Days [177, 190]
	Week 28	Day 197	Days [191, 204]
	Week 30	Day 211	Days [205, 218]
	Week 32	Day 225	Days [219, 232]
	Week 34	Day 239	Days [233, 246]
	Week 36	Day 253	Days [247, 281]
	Week 44	Day 309	Days [282, 337]
	Week 52	Day 365	Days [338, 393]
	Week 64	Day 449	Days [408, 491]
	Week 76	Day 533	Days [492, 575]
	Week 88	Day 617	Days [576, 659]
	Week 100	Day 701	Days [660, 715]
	Week 104/EY	Day 730	Days [716, 772]
	Week 116	Day 814	Days [773, 856]
	Week 128	Day 898	Days [857, 940]
	Week 140	Day 982	Days [941, 1024]
	Week 152	Day 1066	Days [1025, 1080]
	Week 156/EY	Day 1096	Days [1081, 1138]
	Week 168	Day 1180	Days [1139, 1222]
	Week 180	Day 1264	Days [1223, 1306]
	Week 192	Day 1348	Days [1307, 1390]
	Week 204	Day 1432	Days [1391, 1446]
	Week 208/EY	Day 1461	Days [1447, 1503]
	Week 220	Day 1545	Days [1504, 1587]
	Week 232	Day 1629	Days [1588, 1671]
	Week 244	Day 1713	Days [1672, 1755]
	Week 256	Day 1797	Days [1756, 1811]
	Week 260/EY	Day 1826	Days [1812, 1840]
Liver tests, Vital signs, and other central lab tests	Baseline[c]	Day -1	≤ Day 1
	Week 1	Day 8	Days [2, 11]
	Week 2	Day 15	Days [12, 18]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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/EY	Day 730	Days [715, 743]
	Week 110	Day 772	Days [744, 792]
	Week 116	Day 814	Days [793, 835]
	Week 122	Day 856	Days [836, 877]
	Week 128	Day 898	Days [878, 919]
	Week 134	Day 940	Days [920, 961]
	Week 140	Day 982	Days [962, 1003]
	Week 146	Day 1024	Days [1004, 1045]
	Week 152	Day 1066	Days [1046, 1079]
	Week 156/EY	Day 1096	Days [1080, 1117]
	Week 162	Day 1138	Days [1118, 1159]
	Week 168	Day 1180	Days [1160, 1201]
	Week 174	Day 1222	Days [1202, 1243]
	Week 180	Day 1264	Days [1244, 1285]
	Week 186	Day 1306	Days [1286, 1327]
	Week 192	Day 1348	Days [1328, 1369]
	Week 198	Day 1390	Days [1370, 1411]
	Week 204	Day 1432	Days [1412, 1446]
	Week 208/EY	Day 1461	Days [1447, 1482]
	Week 214	Day 1503	Days [1483, 1524]
	Week 220	Day 1545	Days [1525, 1566]
	Week 226	Day 1587	Days [1567, 1608]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 232	Day 1629	Days [1609, 1650]
	Week 238	Day 1671	Days [1651, 1692]
	Week 244	Day 1713	Days [1693, 1734]
	Week 250	Day 1755	Days [1735, 1776]
	Week 256	Day 1797	Days [1777, 1811]
	Week 260/EY	Day 1826	Days [1812, 1840]

[a] Relative to the BMN 270 infusion day (Day 1)

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

[c] Baseline visit value of FVIII activity is defined as the last available measurement prior to BMN 270 infusion excluding those within 72 hours after a FVIII infusion. Baseline visit value of other assessments is defined as the last available measurement prior to BMN 270 infusion.

[d] Baseline value is derived from the period between 12 months prior to 270-303 screening and the BMN 270 infusion day.

EY: end of year visit.

20.2 Preferred Terms Suggestive of Thromboembolic Events

confusional state (10010305)
muscular weakness (10028372)
swelling (10042674)
peripheral swelling(10048959)
odema Peripheral (10030124)
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 (10036653)
headache (10019211)
hypoaesthesia (10020937)
eye pain (10015958)
eye swelling (10015967)
visual impairment (10047571)
visual acuity reduced (10047531)

Every: Approval Task	PI PI PI
Every: Approval Task	PI al Science PI
Every: Approval Task	PI tative PI
Every: Approval Task	PI PI PI
Every: Approval Task	PI PI PI Clinical Science
Every: Approval Task	PI PI PI