Official Title: A Phase 3, Open-Label, Single-Arm Study To Evaluate The Efficacy And Safety Of BMN 270, An Adenovirus-Associated Virus Vector-Mediated Gene Transfer Of Human Factor VIII In Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

NCT Number: NCT03370913

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 13 Dec 2021

BIOMARIN

Note to File (NTF)

Project No.:	BMN 270; Study 270-301
Project Name (If Applicable):	To align the 270-301 Protocol (version 7.0, 15 July 2021; US-specific) and the 2-year analysis SAP (version 2.0, 13 December 2021) with the 2-year 270-301 CSR
Location:	NA
Subject:	NTF to bridge the 270-301 protocol (version 7.0, 15 July 2021; US-specific) and the 2-year analysis SAP (version 2.0, 13 December 2021) with the 2-year 270-301 CSR for primary and secondary endpoints and other changes made to the 2-year analyses.
Date	02 March 2023

Overserved Discrepancy – Primary and secondary endpoints and statistical analysis methods used in the 2-year 270-301 CSR were modified from those specified in the effective versions of the 270-301 protocol (version 7.0, 15 July 2021; US-specific) and the 2-year analysis SAP (version 2.0, 13 December 2021).

Background – The 2-year analysis of Study 270-301 was performed in January 2022 based on pre-specified analysis methods in the 2-year analysis SAP. Type B Pre-BLA feedback was received from FDA on 16 May 2022. FDA requested changes to the analysis methods, including primary and secondary endpoints. The results reported in 2-year 270-301 CSR reflect the modified analysis methods per FDA feedback and this CSR was submitted to the FDA on 29 September 2022, in the BLA re-submission. Changes from the planned analysis methods were documented in Section 9.8.2 of the CSR (Changes to Planned Analyses).

Solution – This NTF serves as a bridging document between the analysis methods in the 270-301 protocol (version 7.0, 15 July 2021; US-specific), the 2-year analysis SAP (version 2.0, 13 December 2021) and the 2-year 270-301 CSR.

The table below outlines all the changes made to the 2-year analysis methods, including primary and secondary endpoints

Changes to planned 2-yr Analyses for 270-301 based on FDA feedback			
	270-301 Protocol (version 7.0, 15 July 2021; US-specific)	**2-year Analysis SAP (version 2.0, 13 December 2021)**	**270-301 2-Year CSR (in response to FDA Feedback)**
Primary and secondary efficacy endpoints	Primary • ABR (treated bleeds) Secondary • FVIII activity • FVIII utilization (If discrepancies exist in statistical methods between the SAP and the study protocol, the SAP will prevail)	Primary • ABR (treated bleeds) Secondary • FVIII activity • FVIII utilization • ABR (all bleeds) • Haemo-QoL-A Total score • Haemo-QoL-A Physical Functioning domain score • Haemo-QoL-A	Primary • ABR (all bleeds) Secondary • ABR (treated bleeds) • FVIII activity • FVIII utilization • Haemo-QoL-A Total score • Haemo-QoL-A Physical Functioning domain score • Haemo-QoL-A Consequences of bleeding domain score

		Consequences of bleeding domain score • Haemo-QoL-A Role functioning domain score	• Haemo-QoL-A Role functioning domain score
Hypothesis testing	Hierarchical testing will be performed in the order of endpoints as shown above, each at the alpha level of 0.0498. (If discrepancies exist in statistical methods between the SAP and the study protocol, the SAP will prevail)	Hierarchical testing will be performed in the order of endpoints as shown above, each at the alpha level of 0.05.	At the time of receipt of FDA WRO feedback, the outcomes of the SAP-specified hypothesis testing were known to the Sponsor - all statistically significant at the alpha level of 0.05. By considering ABR (all bleeds) as the primary efficacy endpoint, the revised analyses will simply present the study results with p-values to show statistical significance on each endpoint.
Ranking of secondary efficacy endpoints	Secondary efficacy endpoints are ranked in hypothesis testing order as shown above. (If discrepancies exist in statistical methods between the SAP and the study protocol, the SAP will prevail)	Secondary efficacy endpoints are ranked in hypothesis testing order as shown above.	Secondary efficacy endpoints are not ranked, and their results will be presented one by one.
Sensitivity analysis: impact of exogenous FVIII product use in the efficacy evaluation period (EEP) on ABR	--	Not planned	The following sensitivity analyses will be performed by counting exogenous FVIII product use in EEP as bleeding events: • #1: count each one-time FVIII prophylaxis use in EEP as one bleed • #2: count each one-time or routine FVIII prophylaxis use in EEP as one bleed #3: count each one-time or routine FVIII prophylaxis use and each surgery/procedure that had FVIII use in EEP as one bleed
Additional sensitivity analysis: impact of IS on ABR and FVIII activity	--	Not planned	The following sensitivity analyses will be performed in subjects who have been off IS for at least 12 months • Repeat the primary analysis of ABR (ABR

			change from baseline) in this subgroup Repeat the primary analysis of FVIII activity (FVIII activity change from baseline at Week 104) in this subgroup
Washout period between the last dose of FVIII prophylaxis following gene therapy and the start of EEP	No washout period	3 days	Based on the half-life of the original FVIII prophylaxis product: • 3 days for standard half-life or plasma-derived products • 5 days for extended half-life
Definition of AEs/SAEs related to IS	--	All AEs/SAEs during or within 2 weeks' post-IS use	All AEs/SAEs following IS use up to each subject's last visit for the analysis
IS (CS or AIS) therapy to be included in the analysis	--	Systemic IS (CS or AIS) indicated for ALT elevation of any duration, or indicated for other purposes with a duration of at least 4 weeks	Systemic IS (CS or AIS) indicated for any purpose of any duration
Definition of an IS course (cycle)	--	The start of an IS use through the end of taper or increase in IS dose for ≥ 2 consecutive weeks preceded by at least 2 decreases in IS dose, whichever occurs earlier	The time period between the first day of starting an IS therapy to the last day of IS use. Any increase in the dose of IS will be considered as a new cycle of IS therapy with the first day of increase of IS dose constituting as the start day of a new cycle.

Comment(s)/ Recommendation(s):
This NTF serves as a bridging document between the analysis methods in the 270-301 protocol (version 7.0, 15 July 2021; US-specific), the 2-year analysis SAP (version 2.0, 13 December 2021) and the 2-year 270-301 CSR.

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STATISTICAL ANALYSIS PLAN FOR TWO-YEAR ANALYSIS
(2-Year Analysis SAP)

Protocol Number: 270-301

Study Title: A Phase 3, Open-Label, Single-Arm Study To Evaluate The Efficacy And Safety Of BMN 270, An Adenovirus-Associated Virus Vector-Mediated Gene Transfer Of Human Factor VIII In Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

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

Version: 2.0

Date: 13 December 2021

APPROVALS

Statistical Analysis Plan for Two-Year Analysis

Title: A Phase 3, Open-Label, Single-Arm Study To Evaluate The Efficacy And Safety Of BMN 270, An Adenovirus-Associated Virus Vector-Mediated Gene Transfer Of Human Factor VIII In Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

Protocol: 270-301

Date: 13 December 2021

Approvals

_____ PI PhD PI, Statistical Science, Biostatistician	___/___/___ DD MM YY
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_____ PI PI, Data Analytics Science Statistical Programmer	___/___/___ DD MM YY
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_____ PI, PhD PI, Statistical Science Head of Statistical Science	___/___/___ DD MM YY
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Please see attached signature page.

1 SAP SYNOPSIS

TITLE OF STUDY: A Phase 3, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Level ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

PROTOCOL NUMBER: 270-301

STUDY OBJECTIVES:

The primary efficacy objective of the study is to:

- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period (from Week 5 post-BMN 270 infusion (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, to last visit by the data cut-off for the 2-year analysis, hereafter referred to as "Post FVIII Prophylaxis to Last Visit")

The secondary efficacy objectives of the study are to:

- Assess the efficacy of BMN 270 (compared to no treatment) defined as FVIII activity, as measured by chromogenic substrate assay, at Week 104 following intravenous infusion of BMN 270
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on usage of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on the number of bleeding episodes (irrespective of exogenous FVIII replacement therapy) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on health-related quality of life patient-reported outcomes (HRQoL PROs: Haemo-QoL-A Total Score; Physical Functioning, Consequences of Bleeding, and Role Functioning domain scores) at Week 104 following intravenous infusion of BMN 270

  Note: While the efficacy evaluation period (EEP) for the primary analysis of the primary efficacy endpoint (annualized bleeding rate, ABR) is specified as "from Week 5 post-BMN 270 infusion (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, to last visit by the data cut-off for the 2-year analysis", additional EEPs will be assessed to comprehensively characterize the subject-level treatment effect of BMN 270 on ABR, taking into consideration the impact of exogenous FVIII and emicizumab use. See Section 13.1 "Efficacy Evaluation Periods" and Section 13.3.5 "Joint Analysis of ABR and Exogenous FVIII/Emicizumab Use" for details.

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on additional HRQoL PROs at Week 104 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the safety of BMN 270 during the first 52 weeks following intravenous infusion of BMN 270
- Assess the long-term safety of BMN 270

The exploratory objectives of the liver biopsy substudy are:

- To examine the histopathology of the liver following BMN 270 therapy, including assessing for possible safety findings (eg, fibrosis, fatty liver disease, lymphocytic invasion)
- To quantify FVIII DNA, RNA, and protein expression within hepatocytes
- To determine which forms of rAAV vector DNA are present at the time of biopsy.
- To determine the distribution of BMN 270-transduced hepatocytes in human liver (ie, peri-portal hepatocytes, central vein hepatocytes)

STUDY DESIGN

This is a Phase 3, single-arm, open-label study in hemophilia A (HA) patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. Subjects were planned to be enrolled at approximately 60 sites worldwide (48 sites actual) and 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.

Approximately 130 adult subjects with severe HA (134 actual) were planned to receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion:

- Directly enrolled subjects: Approximately 20 HIV-negative subjects (22 actual, including 2 HIV-positive subjects who were enrolled prior to Protocol Amendment 3 [dated 24 August 2018] that suspended further enrollment of HIV-positive subjects) were planned to enroll in the study with at least 12 months of retrospectively collected well-documented high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage;
- Study 270-902 rollover subjects: Approximately 110 HIV-negative subjects (112 actual), were planned to enroll in the study after having completed approximately 6 months' participation in the BioMarin-sponsored non-interventional study 270-902, in which bleeding and FVIII use data prior to gene therapy while on FVIII prophylaxis were prospectively collected.

ANALYSIS POPULATIONS

Intention-to-treat (ITT) population: all subjects who received BMN 270 infusion in Study 270-301.

Modified intention-to-treat (mITT) population: subjects who received BMN 270 infusion in Study 270-301 and were HIV-negative at study screening.

Study 270-902 rollover subjects: subjects who completed approximately 6 months' participation in the BioMarin-sponsored non-interventional study 270-902 before enrolling in Study 270-301, were HIV-negative at study screening, and received BMN 270 infusion in Study 270-301.

Directly enrolled subjects: subjects who were directly enrolled in Study 270-301 without prior participation in Study 270-902 and received BMN 270 infusion in Study 270-301.

Directly enrolled, HIV-negative subjects: subjects who were directly enrolled in Study 270-301 and were HIV-negative at study screening.

Study 270-902 rollover subjects will be used for the primary analyses of the primary efficacy endpoint (ABR) and the second-ranked secondary efficacy endpoint (annualized FVIII utilization), the mITT population will be used for the primary analysis of the first-ranked secondary efficacy endpoints (FVIII activity) and the tertiary efficacy endpoints (PROs), 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 all 5 analysis populations for comparison purposes. If not used for the primary analysis, an analysis population may be used in supportive analyses of the efficacy and safety.

When applicable, additional sensitivity analyses will 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.

Exploratory analyses of efficacy and safety may be performed on a subset of subjects with longer follow-up time (eg. 3 years) at the time of the 2-year analysis.

STUDY ENDPOINTS AND ANALYSES:

Primary efficacy endpoint and analyses:

The primary efficacy endpoint is 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 for treated bleeds) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit").

The primary analyses of change from baseline in the ABR for treated bleeds will be based on Study 270-902 rollover subjects. Change from baseline in ABR for treated bleeds will first be tested for non-inferiority with a NI margin of 3.5 using the confidence interval approach. Assuming a t distribution with the variance estimated from the data, a two-sided (1-α)*100% confidence interval (CI) of the mean change (post-baseline - baseline) will be constructed, where the significance level α is determined by the fallback procedure (see Section 13.7for details). If the upper bound of the CI is less than 3.5, the null hypothesis will be rejected and the non-inferiority of BMN270 versus FVIII prophylaxis in ABR for treated bleeds with this margin will be declared. Subsequently, superiority will be assessed using the same CI. The two-sided p-value for superiority will be obtained through a one-sample t-test to test the null hypothesis that the change is 0 or greater.

Supportive analyses will include:

- The number of bleeding episodes requiring exogenous FVIII replacement treatment will be listed by subjects and by periods (pre-BMN 270 infusion [baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, Post FVIII Prophylaxis-52, Weeks 53-104, and the efficacy evaluation periods as defined in Table 13.1.1), and the ABR will be summarized descriptively.
- The analysis of change from baseline in ABR for treated bleeds will also be conducted using data in the efficacy evaluation periods as defined in Table 13.1.1.

The following sensitivity analyses will be performed:

- The primary analysis will be performed on the PP population when applicable.
- The primary analysis will be performed with baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) values calculated using the data 12-months prior to study enrollment.
- The ABR for treated bleeds will 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], Weeks 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 change from baseline in the ABR in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit") will also be tested using Wilcoxon signed-rank test.
- If a subject restarts FVIII prophylaxis, starts emicizumab, or discontinues from the study prior to the data cut-off for he analysis, a sensitivity analysis will be performed where the post-baseline ABR for treated bleeds is imputed as the same as the baseline ABR for treated bleeds (ie, the change in ABR for treated bleeds is 0).

Secondary efficacy endpoints and analyses:

The secondary endpoints are:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Week 104 post-BMN 270 infusion

- 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 to Last Visit")
- 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 therapy (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Total score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Physical Functioning domain score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Consequences of bleeding domain score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Role functioning domain score, at Week 104 post-BMN 270 infusion

The change from baseline in each subject's FVIII activity is defined as the difference between the median of values obtained at Week 104 with the window defined in Appendix 20.1 and the baseline value, which will be imputed as 1 IU/dL for each subject.

The primary analysis of the change from baseline to Week 104 in FVIII activity will be a one-sample t-test on the mITT population. Missing values at Week 104 will be imputed using the imputation methods specified in Section 13.3.1.

Supportive analyses of the FVIII activity level will include:

- The FVIII activity level will be summarized descriptively in 4 or 6-week visit windows with missing data imputed from baseline up to the last possible visit by data cut-off (eg. if a subject was lost to follow-up at Week 60 and would have been followed for 104 weeks by the data cut-off, his FVIII activity levels beyond Week 60 will be imputed to be 0 IU/dL up to Week 104).
- The proportion of subjects whose FVIII activity levels per chromogenic assay are <3 IU/dL, 3-<5 IU/dL, 5-<40 IU/dL, 5-<15 IU/dL, 15-<40 IU/dL, >=40IU/dL, 40-<=150 IU/dL, and >150 IU/dL will be provided for each visit window.
- The maximum of each subject's FVIII activity levels (medians of the values in visit windows defined in Appendix 20.1), and the time to the maximum level, will be summarized descriptively.
- The FVIII activity level will be summarized descriptively at milestone timepoints defined as the end of every 6 months post-BMN 270 infusion (eg, Weeks 23-26, Weeks 49-52, Week 76 and 104 with the visit windows defined in Appendix 20.1). Missing data will be imputed using the imputation methods specified in Section 5.6. In addition, the change in FVIII activity between certain milestone timepoints (eg, between Weeks 23-26 and Weeks 49-52, between Weeks 49-52 and Week 76, between Weeks 49-52 and Week 104) and between Week 104 and the maximal FVIII activity by the Week 104 will also be summarized.

- The primary and supportive analyses described above may be conducted for FVIII activity values by one-stage clotting assay
- The relationship between the FVIII activity values by one-stage clotting and chromogenic assays will be evaluated using regression analysis.

The following sensitivity analyses of the FVIII activity level will be performed:

- The primary analysis with only the observed cases (without imputation of missing values)
- The primary analysis with imputing missing data at Week 104 using last observation carried forward (LOCF) approach
- The primary analysis with imputing missing data at Week 104 to be 0 IU/dL
- The primary analysis performed on the PP population when applicable
- Analysis using the mean rather than the median of the observations within the analysis window, but otherwise the same as the primary analysis
- A mixed model for repeated measures (MMRM) approach using only observed cases of FVIII activity level every 4 weeks performed on the mITT population. In this approach, the model will include visit (every 4 weeks, from baseline to Week 104) as the only factor, and the least squares mean change from baseline to Week 104 will be reported

The primary analysis for the change from baseline in annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will be a one-sample t-test based on study 270-902 rollover subjects to test the null hypothesis that the change from baseline in annualized FVIII utilization is 0 or greater (ie. superiority when the null hypothesis is rejected).

Supportive analyses of annualized FVIII utilization (IU/kg/year) will include:

- The FVIII utilization will be listed by subjects and by periods (pre-BMN 270 infusion[baseline period], Weeks 1-4, Week 1 to end of original FVIII prophylaxis, Weeks Post FVIII Prophylaxis-52, Weeks 53-104, and the efficacy evaluation periods as defined in Table 13.1.1), and the annualized utilization rates will be summarized descriptively.
- The analysis of change from baseline in annualized FVIII utilization will also be conducted using data in the efficacy evaluation periods as defined in Table 13.1.1.

The following sensitivity analyses will be performed:

- The primary analysis will be performed on the PP population when applicable.
- The primary analysis will be performed with baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) values calculated using the data 12-months prior to study enrollment.

The primary analyses for ABR for all bleeds will be performed on the Study 270-902 rollover subjects. The analyses for ABR for all bleeds will be similar as the analyses for ABR for treated bleeds.

The primary analyses of Haemo-QoL-A Total score will be a one-sample t-test based on the mITT population using observed cases. The total score will be summarized descriptively by visits. A graphical summary of mean change over time will be provided. The total score will also be analyzed using an MMRM approach. The model will include visit (baseline, Week 4, Week 12, Week 26,

Week 52, Week 76, Week 104) as the only factor and will use an unstructured covariance matrix. The LS mean change from baseline to Week 104 will be reported.

The analyses for Haemo-QoL-A domain scores (Physical functioning, Consequence of bleeding, Role functioning) will be the same as the Total score analyses.

Additional analyses of efficacy endpoints

Correlation between FVIII activity and bleeding risk

The following analyses will be performed to investigate the correlation between FVIII activity levels and ABR:

- Using a cut-off of FVIII activity level (e.g., 5 IU/dL), each subject's data will be divided into 3 periods: baseline, from Week 5 to the first time reaching 5 IU/dL, and from the first time reaching 5 IU/dL to the end of the efficacy evaluation period. For each period, the duration of the period, the number of treated bleeds, the ABR, and the change in ABR from baseline will be listed and summarized.
- Based on the FVIII activity visit windows (Appendix 20.1 Visit Windows), median FVIII activity and total number of treated bleeds (defined in Section 13.2) will be calculated for each window for every subject. The total number of treated bleeds in each window will be plotted against the corresponding FVIII activity level to show the FVIII activity level around the time of bleeding. In addition, a negative binomial regression will be performed, using the number of treated bleeds in each window and the FVIII activity level in the window to model the relationship between the FVIII activity level and ABR. The SAS GENMOD procedure will be used where a REPEATED statement is included to account for within-subject correlation.
- ABR will be summarized in subgroups of subjects determined by the FVIII activity levels measured at Weeks 23-26, Weeks 49-52, Week 104, as well as by the peak FVIII activity levels.

Joint analysis of ABR and exogenous FVIII/emicizumab use

Per the study protocol, subjects will discontinue their regular prophylactic FVIII treatment regimen starting Week 5 post the day of BMN 270 infusion and switch to an episodic treatment schedule. In addition, subjects who experience recurrent bleeding episodes may resume their prior FVIII prophylaxis or start prophylactic emicizumab treatment. Because ABR and exogenous FVIII/emicizumab use are not independent, the following analyses will be performed to jointly assess ABR and exogenous FVIII/emicizumab use:

- Paired analysis of ABR and exogenous FVIII/emicizumab use in each of the efficacy evaluation periods defined in Section 13.1. This analysis enables the interpretation of ABR in the context of exogenous FVIII/emicizumab use.
- Summary of ABR in subgroups of subjects determined by the level of exogenous FVIII/emicizumab use:

- Subjects who did not resume exogenous FVIII/emicizumab prophylaxis
  - Subjects with zero FVIII infusions
  - Subjects with at least one FVIII infusion
- Subjects who resumed FVIII/emicizumab prophylaxis
  - Subjects who resumed FVIII prophylaxis
  - Subjects who resumed emicizumab prophylaxis

FVIII activity and ABR in immunosuppression-free periods

To investigate potential confounding effects of immunosuppressant use on the treatment effect of BMN 270, FVIII activity and ABR in immunosuppression-free periods will be assessed. The immunosuppression-free period is defined as the efficacy evaluation period for subjects who never received immunosuppressants (i.e., systemic corticosteroids or alternative immunosuppressants) and the efficacy evaluation period after the immunosuppressant has been discontinued for subjects who did receive immunosuppressants. The efficacy evaluation period starting from the date of the first immunosuppressant use through the date of the last immunosuppressant use is considered as the immunosuppression period. For subjects who received and then discontinued immunosuppressants, their ABR in the immunosuppression-free period will be compared to their ABR in the immunosuppression period. This comparison will be repeated for subjects whose immunosuppression-free period is at least one year vs. less than one year. The number of subjects who were off immunosuppressants at various timepoints (e.g. 3, 6, 9, 12, 18, 24 months, etc.) and the corresponding ABR will also be summarized.

For comparison purposes, FVIII activity levels over time and ABR in the efficacy evaluation period will be summarized for subjects who never received immunosuppressants and subjects who were still on immunosuppressants at the time of the data cut-off for the 2-year analysis.

Impact of cessation of immunosuppressant or select concomitant medication use on FVIII expression

The impact of cessation of immunosuppressant use on FVIII expression will be evaluated in the mITT subjects who have discontinued immunosuppressant therapy before the data cut-off date for the 2-year analysis. To account for time factor, subjects will be divided into subgroups based on their timing of immunosuppressant discontinuation (Weeks 14-26, 27-39, 40-52, et al.). Each subject's median FVIII activity level in the 4 weeks immediately after immunosuppressant discontinuation will be compared to that immediately prior. The median change in FVIII activity will be plotted against the median time to immunosuppressant discontinuation in each of the subgroups.

For comparison purposes, similar analyses will be performed to assess the natural decline of FVIII activity while subjects are on or off immunosuppressants. Changes in FVIII activity levels between 4 weeks before and 4 weeks after Week 20, 24, 28, et al. will be plotted separately for subjects who ever or never received immunosuppressant therapy.

The above analyses will be repeated for select concomitant medications (e.g., lamivudine) to assess the impact of such on FVIII expression in the mITT subjects who have discontinued them before the data cut-off date for the 2-year analysis.

Time to first treated bleed and restart of prophylactic treatment

Time to first treated bleed will be calculated for baseline and Post FVIII Prophylaxis-last visit periods for study 270-902 rollover subjects. Subjects who have zero treated bleeds in the baseline and Post FVIII Prophylaxis-last visit periods will be censored at the BMN 270 infusion date and the

last visit date, respectively. Time to first treated bleed will be summarized with Kaplan-Meier (KM) curves and KM quartiles (when estimable) for baseline and Post FVIII Prophylaxis-last visit periods. Two-sided 95% confidence intervals will be provided for KM quartiles (Klein and Moeschberger, 1997).

Time to first spontaneous treated bleed will be calculated and summarized in the same way as for time to first treated bleed.

Time to restart of prophylactic treatment will be calculated for the Post FVIII Prophylaxis-last visit period for all subjects. The definition of restart of prophylactic treatment is provided in Section 13.1. Subjects who remain on episodic treatment post-BMN 270 will be censored at the last visit date. Kaplan-Meier (KM) curve, KM quartiles (when estimable) and associated 2-sided 95% confidence intervals will be provided for time to restart of prophylactic treatment. If the number of subjects who restart prophylactic treatment is small (eg, < 5), their time to restart of prophylactic treatment will be listed instead.

Time to restart of prophylactic treatment or the first of ≥2 spontaneous treated bleeds ≤26 weeks apart (where the first spontaneous treated bleed occurred after two consecutive FVIII activity levels <5 IU/dL, based on chromogenic assay) will be calculated for the Post FVIII Prophylaxis-last visit period for all subjects. It will be summarized in the same way as for time to restart of prophylactic treatment.

Interim analysis and multiplicity adjustment

Prior to this 2-year analysis, two protocol-specified interim analyses and a 1-year analysis were planned, of which one interim analysis and the 1-year analysis were performed.

Two interim analyses were planned after approximately 16 and 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued study prior to Week 26), respectively. The concept of the interim analyses was to facilitate initiation of regulatory review of the ongoing study in the event that robust improvements (essentially normalization) in Factor VIII activity in a sufficient proportion of the subjects are observed. The primary efficacy endpoint was subject's FVIII response status, where a subject was considered as a responder if the median FVIII activity per chromogenic assay during Weeks 23-26 post-BMN 270 infusion is ≥ 40 IU/dL. The alpha levels of 0.0002 and 0.001 were allocated to the first and second interim analysis, respectively. The second interim analysis would only occur if the result from the first interim analysis was not positive (i.e., if the pre-specified statistical significance was not achieved). A 1-year analysis was planned after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study prior to Week 52). The efficacy endpoints included change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in ABR for treated bleeds, change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity per chromogenic assay at Weeks 49-52, and change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in annualized FVIII utilization. These endpoints were tested sequentially using a hierarchical testing procedure at the alpha level determined by the fallback procedure (Wiens, 2005) to control the family-wise type I error rate at 0.05. Results from this analysis were intended to support regulatory submissions to EMA and other health authorities outside of FDA.

The first interim analysis was performed in May 2019 (data cut-off date: 30 April 2019) after 16 directly enrolled, HIV-negative subjects have completed the Week 26 visit. Based on the analysis results (p=0.001) and the totality of the data, the secondary interim analysis was deemed unnecessary (the test would be statistically significant at the pre-specified significance level of 0.001) and therefore never implemented. The 1-year analysis was performed in January 2021 (data cut-off date: 16 November 2020) after all subjects had been followed for 52 weeks post-BMN 270 infusion. Results from all pre-specified tests were statistically significant ($p < 0.0001$) at the alpha level of 0.0498 that was determined by the fallback procedure (SAP version 3.0, dated 17 December 2020).

As specified in the 1-year analysis SAP (version 3.0, dated 17 December 2020), in the event that a 2-year final analysis is necessary, the hierarchical testing procedure used in the 1-year analysis will be extended to the 2-year final analysis. That is, when all pre-specified tests (ie. non-inferiority test of BMN 270 vs. FVIII prophylaxis in ABR with a NI margin of 3.5, superiority test of BMN 270 vs. no treatment for severe hemophilia A in FVIII activity, superiority test of BMN 270 versus FVIII prophylaxis in FVIII utilization, superiority test of BMN 270 vs. FVIII prophylaxis in ABR) are statistically significant at the 1-year analysis, the corresponding efficacy endpoints at 2 years will be tested in the same sequence. Per FDA's recommendation, the 2-year final analysis will be performed at the significance level of 0.05. The efficacy endpoints will be tested in the following hierarchical testing sequence:

1. For non-inferiority of BMN 270 versus FVIII prophylaxis in ABR (treated bleeds) with a NI margin of 3.5

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 3.5

2. For superiority of BMN 270 versus no treatment for severe hemophilia A in FVIII activity

   Null hypothesis: FVIII activity at Week 104 – baseline FVIII activity ≤ 0

3. For superiority of BMN 270 versus FVIII prophylaxis in FVIII utilization

   Null hypothesis: post-baseline FVIII utilization – baseline FVIII utilization ≥ 0

4. For superiority of BMN 270 versus FVIII prophylaxis in ABR (treated bleeds)

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 0

5. For superiority of BMN 270 versus FVIII prophylaxis in ABR (all bleeds)

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 0

6. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Total score

   Null hypothesis: post-baseline total score at Week 104 – baseline total score ≤ 0

7. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Physical functioning domain score

   Null hypothesis: post-baseline physical functioning score at Week 104 – baseline physical functioning score ≤ 0

8. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Consequences of bleeding domain score

   Null hypothesis: post-baseline Consequences of bleeding score at Week 104 – baseline Consequences of bleeding score ≤ 0

9. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Role functioning domain score

   Null hypothesis: post-baseline Role functioning score at Week 104 – baseline Role functioning score ≤ 0

After the 2-year final analysis, safety and efficacy will then continue to be assessed long-term in all subjects for a total of approximately 5 years.

Safety endpoints and analyses

- Incidence of adverse events (AEs) and serious AEs (SAEs)
- Change in clinical laboratory tests (serum chemistry and hematology)
- Change in vital signs
- Change in physical examination
- Vector shedding (blood, urine, semen, stool, saliva)
- Liver tests (LTs, including ALT, AST, GGT, direct and total bilirubin, lactate dehydrogenase [LDH], and alkaline phosphatase)
- Immune response to FVIII transgene product and AAV5 capsid proteins

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, serious adverse events (SAEs), SAEs assessed by the investigator as related to BMN 270, AEs leading to study discontinuation, deaths, AEs related to immunosuppression 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. A by-subject listing will be provided for subjects who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study.

Vector integration and insertional mutagenesis risk of BMN 270 will be assessed separately in non-clinical reports.

Assessments of concomitant medications on FVIII activity levels and ALT elevations post-BMN 270 infusion will be descriptive based on the mITT population.

Clinical laboratory tests, vital signs, vector shedding and immune response parameters 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.

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.

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AAV	Adeno-associated virus
ABR	Annualized bleeding rate
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BLA	Biologics License Application
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CI	Confidence interval
CRF	Case report form
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
EEP	Efficacy evaluation period
EMA	European Medicines Agency
EOSI	Events of special interest
ETV	Early termination visit
FDA	Food and Drug Administration
FVIII	Coagulation factor VIII
FXa	Coagulation factor Xa
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HA	Hemophilia A
hFVIII	Human coagulation factor VIII
HLT	High Level Term
HRQoL	Health-related quality of life
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
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
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
rhFVIII	Recombinant human FVIII protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SFU	Spot-forming units
SMQ	Standardized MedDRA query
SOC	System organ class
TAb	Total antibody
TEAE	Treatment-emergent adverse event
TI	Transduction Inhibition
TLGs	Tables, listings, and graphs
VAS	Visual analog scale
vg	Vector genomes
WHO	World Health Organization

4 INTRODUCTION

This document describes the statistical methods to be implemented in the analysis of 2-year data collected under clinical study protocol 270-301 (Amendment 7, United States Specific, 15 July 2021), "A Phase 3, Open-Label, Single-Arm Study To Evaluate The Efficacy And Safety Of BMN 270, An Adenovirus-Associated Virus Vector-Mediated Gene Transfer Of Human Factor VIII In Hemophilia A Patients With Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions". This SAP (2-Year Analysis SAP) contains definitions of analysis populations, derived variables, and statistical methods for the analyses of efficacy and safety.

4.1 Study Overview and Objectives

Study 270-301 is a Phase 3, single-arm, open-label study designed to assess, in an expanded sample, whether BMN 270 can safely alter the clinical phenotype of hemophilia A patients with residual FVIII activity ≤ 1 IU/dL.

The primary efficacy objective of the study is to:

- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on the number of bleeding episodes requiring exogenous FVIII replacement therapy in the efficacy evaluation period (from Week 5 post-BMN 270 infusion (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, to last visit by the data cut-off for the 2-year analysis, hereafter referred to as "Post FVIII Prophylaxis to Last Visit")

The secondary efficacy objectives of the study are to:

- Assess the efficacy of BMN 270 (compared to no treatment) defined as FVIII activity, as measured by chromogenic substrate assay, at Week 104 following intravenous infusion of BMN 270
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on usage of exogenous FVIII replacement therapy in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on the number of bleeding episodes (irrespective of exogenous FVIII replacement therapy) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")
- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on health-related quality of life patient-reported outcomes (HRQoL PROs: Haemo-QoL-A Total Score; Physical Functioning, Consequences of Bleeding, and Role Functioning domain scores) at Week 104 following intravenous infusion of BMN 270

Note: While the efficacy evaluation period (EEP) for the primary analysis of the primary efficacy endpoint (annualized bleeding rate, ABR) is specified as "from Week 5 post-BMN 270 infusion (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, to last visit by the data cut-off for the 2-year analysis", additional EEPs will be assessed to comprehensively characterize the subject-level treatment effect of BMN 270 on ABR, taking into consideration the impact of exogenous FVIII and emicizumab use. See Section 13.1 "Efficacy Evaluation Periods" and Section 13.3.5 "Joint Analysis of ABR and Exogenous FVIII/Emicizumab Use" for details.

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 (compared to FVIII prophylaxis) on additional HRQoL PROs at Week 104 following intravenous infusion of BMN 270

The safety objectives of the study are to:

- Evaluate the safety of BMN 270 during the first 52 weeks following intravenous infusion of BMN 270
- Assess the long-term safety of BMN 270

The exploratory objectives of the liver biopsy substudy are:

- To examine the histopathology of the liver following BMN 270 therapy, including assessing for possible safety findings (eg, fibrosis, fatty liver disease, lymphocytic invasion)
- To quantify FVIII DNA, RNA, and protein expression within hepatocytes
- To determine which forms of rAAV vector DNA are present at the time of biopsy.
- To determine the distribution of BMN 270-transduced hepatocytes in human liver (ie, peri-portal hepatocytes, central vein hepatocytes)

4.2 Study Design

This is a Phase 3, single-arm, open-label study in hemophilia A (HA) patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. Subjects were planned to be enrolled at approximately 60 sites worldwide (48 sites actual).

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.

Approximately 130 adult subjects with severe HA (134 actual) were planned to receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion. Approximately 20 HIV-

negative subjects (22 actual, including 2 HIV-positive subjects who were enrolled prior to Protocol Amendment 3 [dated 24 August 2018] that suspended further enrollment of HIV-positive subjects) were planned to enroll in the study with at least 12 months of retrospectively collected well-documented, high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage, while approximately 110 HIV-negative subjects (112 actual) were planned to enroll in the study after having completed at least 6 months' participation in the BioMarin-sponsored non-interventional Study 270-902, in which bleeding and FVIII use data prior to gene therapy while on FVIII prophylaxis were prospectively collected.

In order to minimize bias in the 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, has been convened. The DMC has sole access during the trial to amalgamated FVIII activity levels, FVIII usage, and bleeding data, reviews available safety and efficacy (e.g., FVIII activity) data during the study on an ongoing basis, and may determine, based on emerging data and the risk/benefit profile, that further enrollment at 6E13 vg/kg should be discontinued in favor of a different dose of BMN 270, not to exceed 6E13 vg/kg. If the DMC recommends a dosing modification, then additional subjects may be enrolled, up to a total of approximately 130 subjects, at the new BMN 270 dose level (regardless of the number of subjects previously enrolled at 6E13 vg/kg).

Two interim analyses were planned after approximately 16 and 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26), respectively. The second interim analysis would only occur if the result from the first interim analysis was not positive (i.e., if the pre-specified statistical significance was not achieved). A 1-year analysis was planned after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study prior to Week 52). Prior to this planned 2-year analysis, of above two protocol-specified interim analyses and the planned 1-year analysis, the first interim analysis and the one-year analysis were performed in May 2019 (data cut-off date: 30 April 2019) and January 2021 (data cut-off date: 16 November 2020), respectively.

The final analysis based on the 2-year data for the study will be performed after all subjects have been followed for 104 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 104). After the 2-year final analysis, safety and efficacy will then continue to be assessed long-term 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 hemophilia A and residual FVIII levels ≤ 1 IU/dL as evidenced by their medical history.
- Must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and FVIII usage over the previous 12 months must be available.

Subjects were not eligible for this study if they met any of the following key exclusion criteria:

- Detectable pre-existing antibodies to the AAV5 capsid.
- Any evidence of active infection or any immunosuppressive disorder, including HIV infection.

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

4.4 Study Dosage and Administration

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

4.5 Sample Size Determination

Approximately 130 subjects (134 actual) were planned to be dosed in the study. The sample size for this study was based on clinical and statistical considerations in order to provide sufficient data to assess both safety and efficacy of BMN 270.

For the primary endpoint of change from baseline in ABR for treated bleeds, the primary analysis will be performed utilizing bleeding episode data from the study 270-902 rollover subjects. For the analytic sample size calculation of ABR, it is assumed that the pre- and post-BMN 270 infusion population mean ABRs are 3.5 and 1 respectively, and the distribution of ABRs is negative binomial distribution with a dispersion parameter of 2.2. Given the underlying negative binomial distributions, the standard deviations of the pre- and post-BMN 270 infusion ABRs are calculated as 7.8 and 1.8, respectively. The mean (SD) of the change from the pre- to post-BMN 270 infusion ABRs are calculated as -2.5 (8), assuming the correlation between pre- and post-BMN 270 infusion ABRs is zero. Under this assumption, an analytic sample size of 110 will have at least 95% power to demonstrate that the change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in ABR during Post FVIII Prophylaxis to last visit is less than 3.5 (non-inferiority margin), using a one-sample t-test with a 2-sided significance level of 0.05. Under the same

assumptions, a sample size of 110 will have approximately 90% power to demonstrate that the change is less than 0, i.e., superiority of BMN 270 against FVIII prophylaxis.

For the first-ranked secondary endpoint of change from baseline in FVIII activity at Week 104, the primary analysis will be performed utilizing FVIII activity data from the mITT population. A sample size of 130 subjects will provide at least 95% power to demonstrate that the change from baseline (imputed to be 1 IU/dL under no treatment) in FVIII activity at Week 104 is greater than 0, assuming an effect size of 0.6, using a one-sample t-test with a 2--sided significance level of 0.05.

For the second-ranked secondary endpoints of change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy during Post FVIII Prophylaxis to last visit, the primary analysis will be performed utilizing exogenous FVIII use data from the study 270-902 rollover subjects. An analytic sample size of 110 will provide at least 95% power to demonstrate that 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 during Post FVIII Prophylaxis to last visit is less than 0, assuming an effect size of 0.6 conservatively, using one-sample t-test with a 2-sided significance level of 0.05.

Regarding the non-inferiority test for change in ABR for treated bleeds, in the pivotal studies of recently approved FVIII replacement products, the estimated ABRs are consistent across different studies and products. The mean ABRs of prophylactic treatment groups range from approximately 3 to 6, and the mean ABRs of episodic treatment groups range from approximately 30 to 60. The non-inferiority margin of 3.5 is chosen to preserve 90% of the efficacy of prophylactic over episodic treatment, justified by potential advantages of BMN 270 over FVIII replacement therapy. Advantages observed in the 6E13 vg/kg cohort of Study 270-201 include:

- Achieved therapeutic FVIII activity levels with near elimination of bleeding episodes
- Virtual elimination of the need for FVIII replacement therapies
- Improved quality of life

If the DMC recommends a dosing modification, then additional subjects may be enrolled, up to a total of approximately 130 subjects, at the new BMN 270 dose level (regardless of the number of subjects previously enrolled at 6E13 vg/kg).

4.6 Randomization Methods and Blinding

Study 270-301 is a single-arm open-label study. No randomization or blinding was performed. However, to protect trial integrity in a single-arm and open-label setting, role-based access control to subject-level data as well as aggregated summaries have been implemented through a data access plan from the first patient dosed through the final database lock for the 2-year final analysis at Week 104. The data access plan has restricted BioMarin study team members' access to both local and central FVIII activity results (the first-ranked secondary efficacy endpoint), and has only granted limited BioMarin personnel access to the bleeding log and usage of exogenous FVIII replacement therapy (the primary efficacy endpoint and the second-ranked secondary efficacy endpoints) for data cleaning purposes. Those who have access to the primary and secondary endpoints will not make or influence decisions that would alter the study design or the collection or analysis of the primary and secondary efficacy variables, so as to minimize bias in the interpretation of the study's key efficacy results at the interim (Week 26), the 1-year analysis (Week 52) and 2-year final analysis (Week 104).

Given the BioMarin study team's limited access to the study data, the DMC has been convened to review emerging safety and efficacy data, evaluate comparability of drug manufacturing lots within 270--301 and between 270-201 and 270-301, review interim analysis results, and make recommendations regarding the conduct of this study. For additional details on DMC operations and data access control guidelines, please refer to the Study 270-301 DMC charter and the Study 270-301 Data Access Plan, respectively.

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

Intention-to-treat (ITT) population: all subjects who received BMN 270 infusion in 270-301.

Modified intention-to-treat (mITT) population: subjects who received BMN 270 infusion in 270-301 and were HIV-negative at study screening.

Study 270-902 rollover subjects: subjects who completed approximately 6 months' participation in the BioMarin-sponsored non-interventional study 270-902 before enrolling in 270-301, were HIV-negative at study screening, and received BMN 270 infusion in 270-301.

Directly enrolled subjects: subjects who were enrolled in 270-301 without prior 270-902 participation and received BMN 270 infusion in 270-301.

Directly enrolled, HIV-negative subjects: subjects who were directly enrolled in 270-301 and HIV-negative at study screening.

Study 270-902 rollover subjects will be used for the primary analysis of the primary efficacy endpoint and the second-ranked secondary efficacy endpoint of annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy, the mITT population will be used for the primary analysis of the first-ranked secondary efficacy endpoint of FVIII activity based on the chromogenic substrate assay and tertiary efficacy endpoints, 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 all 5 analysis populations for comparison purposes. If not used for the primary analysis, an analysis population may be used in supportive analyses of the efficacy and safety, as specified in Sections 13 and 14.

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 lock and documented in the clinical study report (CSR).

In addition, exploratory analyses of efficacy and safety may be performed on a subset of subjects with longer follow-up time (eg, 3 years) at the time of the 2-year analysis.

5.2 Treatment Group Presentation

In general, if more than one dose level is used in this 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 on study days, wherever applicable. An assessment for a subject will be classified according to the study day of the assessment where it falls within a given window (see Appendix 20.1 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 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 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 data during the specified period prior to enrollment as described in Section 13.3.

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 value of other assessments is defined as the last available measurement prior to the administration of study drug 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 in the visit windows as defined in Section 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 on study, missing FVIII activity values (eg, 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.

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 and number and percentage of screen failures by screen failure reason will be summarized for all subjects screened. The number of subjects enrolled and the number and percentage by reason for subjects enrolled but not treated will be provided. 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, prior to the Week 104 visit or during long-term follow-up, the primary reason for discontinuation will be summarized. The number and percentage of subjects who are continuing the study, who completed Week 52, and who completed Week 104 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 (year)
- 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 (year)
    - type of FVIII treatment for hemophilia A (prophylaxis/episodic)
    - 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) excluding values within 72 hours after a FVIII infusion

And for the following parameters, two sets of analyses will be performed to include data approximately 6-months (starting from Day 1 visit in study 270-902) or 12-months (starting from 6 months before Day 1 visit in study 270-902) prior to 270-301 study enrollment for study 270-902 rollover subjects, separately:

- duration of baseline data collection periods, months
- baseline annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy
- baseline annualized number of FVIII infusions (infusions/year)
- baseline ABR (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 and within 30 days prior to screening;
- concomitant medication—any medication taken after the initiation of the investigational product.

When a medication starts prior to the initiation of the investigational product and continues while on study, it will be summarized as both 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 time to corticosteroid course(s), and number of corticosteroid courses will be summarized for therapeutic purposes. Non-steroidal immunosuppressants may be summarized as well.

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

Subjects who resume prophylactic treatment post BMN 270 infusion will be listed separately.

12 EXTENT OF EXPOSURE TO STUDY DRUG

Each subject receive a single intravenous infusion of BMN 270, and the volume of infusion depended 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 investigational product 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. Estimand formulation is provided for the primary endpoint.

Two interim analyses were planned when approximately 16 and 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued study prior to Week 26), respectively. For controlling the probability of a type I error for the interim analyses, the 1-year analyses, and the 2-year final analyses of the primary efficacy endpoint, the fallback procedure was used. See Section 13.7 for additional information regarding the interim analyses and multiplicity adjustment.

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 purpose of primary data analysis, the efficacy evaluation period for

- Efficacy endpoints such as ABR, number of treated bleeds, annualized FVIII utilization, annualized FVIII infusions and PROs: will be defined as starting from Week 5 post-BMN 270 dosing (Study Day 33) or 3 days after the end of FVIII prophylaxis, 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 dosing (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 dosing (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 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 the purpose of 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 cut-off 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 2 days after end of FVIII prophylaxis, whichever is later).

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

Table 13.1.1: Efficacy Evaluation Periods for Analyses of Primary and Second-Ranked Secondary Efficacy Endpoints

Efficacy Evaluation Period	Start Point	End Point	Analysis
Post-FVIII prophylaxis period	Start of Week 5 post-BMN 270 infusion or 3 days after end of FVIII prophylaxis, whichever is later	Last visit by data cut-off	Primary, t-test
Post-FVIII prophylaxis – week 104	Start of Week 5 post-BMN 270 infusion or 3 days after end of FVIII prophylaxis, whichever is later	Last visit by data cut-off or end of Week 104 post-BMN 270 infusion, whichever is earlier	Supportive, t-test
Post-FVIII prophylaxis – restart of prophylactic treatment up to Week 104	Start of Week 5 post-BMN 270 infusion or 3 days after end of FVIII prophylaxis, whichever is later	Last visit by data cut-off, end of Week 104 post-BMN 270 infusion or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, t-test
Post-FVIII prophylaxis – restart of prophylactic treatment up to last visit	Start of Week 5 post-BMN 270 infusion or 3 days after end of FVIII prophylaxis, whichever is later	Last visit by data cut-off or 1 day before restart of prophylactic treatment, whichever is earlier	Supportive, t-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(s)

The primary efficacy endpoint is:

- 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 for treated bleeds) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")

The annualized number of bleeding episodes for treated bleeds, or annualized bleeding rate for treated bleeds (ABR for treated bleeds) is defined as

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

The primary analyses for the primary endpoints will be performed on the Study 270-902 rollover subjects.

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

- For the primary analysis, the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit") as defined in Section 13.1.
- For the supportive analyses, the efficacy periods as defined in Section 13.1.

The calculation period for the baseline value is defined in the following:

- For the primary analysis, the calculation period is approximately 6 months in the non-interventional study 270-902; i.e., the baseline values will be derived from the prospectively collected 6-month data in 270-902 up until the BMN 270 infusion date in 270-301.
- For the sensitivity analysis, the calculation period is approximately 12 months prior to study screening up until the BMN 270 infusion date in 270-301. For subjects enrolled from Study 270-902, these 12 months of data consist of approximately 6 months of data prospectively collected during 270-902, together with the preceding historical data prior to 270-902 enrollment. For subjects not entering from 270-902, the 12-month historical data prior to 270-301 study screening up until the BMN 270 infusion date will be used.

For the primary efficacy endpoint, only treated bleeds will be considered. Bleeds due to surgery/procedure are not included in the primary efficacy endpoint. 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.

13.2.1 Primary Estimand

The estimand formulation for the primary efficacy endpoint is as follows:

Treatment

(BMN 270 gene therapy + rescue therapy) vs. (FVIII prophylaxis + rescue therapy)

The rescue therapy for the BMN 270 gene therapy includes FVIII infusions for different purposes (routine prophylaxis, one-time prophylaxis, treatment for bleeds, and for surgery/procedure) and the emicizumab prophylaxis for hemophilia A.

The rescue therapy for FVIII prophylaxis includes FVIII infusions for other purposes (one-time prophylaxis, treatment for bleeds, and for surgery/procedure).

Population

HIV-negative subjects with severe hemophilia A

Variable (endpoint)

ABR (treated bleeds)

Intercurrent events and strategies

Intercurrent Events		Strategies for Addressing Intercurrent Events				
		Treatment Policy Strategy	Hypothetical Strategies	Composite Variable Strategies	While-on-Treatment Strategies	Principal Stratum Strategies
Death (unrelated to study drug)					✓	
Lost to follow-up					✓	
FVIII infusions	Started routine prophylaxis	✓				
	One-time prophylaxis	✓				
	Treatment for bleeds	✓				
	For surgery/procedure	✓				
Started emicizumab prophylaxis		✓				

Population-level summary

Mean ABR (treated bleeds) change from baseline

13.2.2 Primary Analysis Method for Primary Efficacy Endpoint

The primary analysis for change from baseline in ABR for treated bleeds will be based on the Study 270-902 rollover subjects. Change from baseline in ABR (ie. post-baseline ABR – baseline ABR) will first be tested for non-inferiority with a NI margin of 3.5 using the confidence interval approach. The non-inferiority test hypotheses are:

H_0 (null hypothesis): Change >= 3.5 versus H_1 (alternative hypothesis): Change < 3.5.

Assuming a t distribution with the variance estimated from the data, a two-sided (1-α)*100% confidence interval (CI) of the mean change will be constructed, where the significance level α is determined by the fallback procedure. See Section 13.7 for details. If the upper bound of the CI is less than 3.5, the null hypothesis will be rejected and the non-inferiority of BMN270 versus FVIII prophylaxis in ABR with this margin will be declared. Subsequently, superiority will be assessed using the same CI. The two-sided p-value for superiority will be obtained through a one-sample t-test to test the null hypothesis that the change is 0 or greater.

If the value is missing, e.g., when a subject drops out before Week 5, the change in ABR will be imputed as the median value of the changes of all subjects' observed cases. See Table 13.2.4.1 for sensitivity analyses with other missing data imputation methods.

13.2.3 Supportive Analysis Methods for Primary Efficacy Endpoint

The number of bleeding episodes 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, Post FVIII Prophylaxis-52, Weeks 53-104, and the efficacy evaluation periods as defined in (Table 13.1.1), and the ABR for treated will be summarized descriptively.

The analysis of change from baseline in ABR for treated bleeds will also be conducted using data in the efficacy evaluation periods as defined in Table 13.1.1.

13.2.4 Sensitivity Analysis Methods for Primary Efficacy Endpoint

The primary analysis will be conducted for the PP population when applicable.

If a subject restarts FVIII prophylaxis, starts emicizumab, or discontinues from the study prior to the cut-off for the analysis, a sensitivity analysis will be performed where the post-baseline ABR for treated bleeds is imputed as the same as the baseline ABR for treated bleeds (ie, the change in ABR is 0).

The primary analysis will also be performed with baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) values calculated using the data starting from 12 months prior to study enrollment. P-values will be provided for descriptive purpose only.

The ABR for treated bleeds will 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], Weeks 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. In addition, the change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in the ABR for treated bleeds in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit") will also be tested using Wilcoxon signed-rank test.

The details of the sensitivity analyses are listed in Table 13.2.4.1.

Table 13.2.4.1: Primary and Sensitivity Analyses of Primary Efficacy Endpoints

Endpoint	Analysis	Analysis population	Analysis period	Imputation	Analysis method
The change from baseline in the ABR for treated bleeds during Post FVIII Prophylaxis-last visit by the data cut-off for the 2-year analysis post-BMN 270 infusion	Primary	Study 270-902 rollover subjects	Baseline: Day 1 visit in 270-902 to BMN 270 infusion in 270-301 (approximately 6 months) On study: starting from week 5 post-BMN 270 dosing (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, until subjects complete the study, reach the last visit by data cut-off for the analysis, or withdraw from the study (ETV), whichever is the earliest.	If ABR for treated bleeds Post FVIII Prophylaxis period is missing, the change in ABR will be imputed as the median value of the changes of all subjects' observed cases (This was for planning purposes. Since all subjects have Post FVIII Prophylaxis ABR for treated bleeds data, no imputation will be carried out).	2-sided t-test
	Sensitivity analysis 1	Per-protocol population	Same as primary	Same as primary	Same as primary
	Sensitivity analysis 2	Same as primary	Baseline: 6 months prior to Day 1 visit in 270-902 to BMN 270 infusion in 270-301 (approximately 12 months) On-study: same as primary	Same as primary	Same as primary
	Sensitivity analysis 3	Same as primary	same as primary	Same as primary	Negative binomial regression model
	Sensitivity analysis 4	Same as primary	same as primary	Same as primary	Wilcoxon signed-rank test
	Sensitivity analysis 5	Same as primary	same as primary	If a subject restarts FVIII prophylaxis or starts emicizumab, the change in ABR for treated bleeds will be imputed as 0.	Same as primary

13.3 Secondary Efficacy Endpoints

The first-ranked secondary efficacy endpoint is:

- The change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity, as measured by chromogenic substrate assay, at Weeks 104 post-BMN 270 infusion

Each subject's FVIII activity level at Week 104 is defined as the median of the values obtained at Week 104 with the window 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 second-ranked secondary efficacy endpoint is:

- 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 to Last Visit")

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 primary analyses for the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will be performed on the Study 270-902 rollover subjects.

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

- For the primary analysis, the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit") as defined in Section 13.1.
- For the supportive analyses, the efficacy periods as defined in Section 13.1.

The calculation period for the baseline value is defined in the following:

- For the primary analysis, the calculation period is approximately 6 months in the non-interventional study 270-902; i.e., the baseline values will be derived from the prospectively collected 6-month data in 270-902 up until the BMN 270 infusion date in 270-301.

- For the sensitivity analysis, the calculation period is approximately 12 months prior to study screening up until the BMN 270 infusion date in 270-301. For subjects enrolled from Study 270-902, these 12 months of data consist of approximately 6 months of data prospectively collected during 270-902, together with the preceding historical data prior to 270-902 enrollment. For subjects not entering from 270-902, the 12-month historical data prior to 270-301 study screening up until the BMN 270 infusion date will be used.

The third-ranked secondary efficacy endpoint is:

- 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 therapy (annualized bleeding rate, ABR for all bleeds) in the efficacy evaluation period ("Post FVIII Prophylaxis to Last Visit")

The annualized number of bleeding episodes for all bleeds, or annualized bleeding rate (ABR for all bleeds) is defined as

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

The primary analyses for ABR for all bleeds will be performed on the Study 270-902 rollover subjects. The calculation periods for the baseline and post-baseline values are similar as the periods of the ABR for treated bleeds

The fourth-ranked to seventh-ranked secondary efficacy endpoints are:

- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Total score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Physical Functioning domain score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Consequences of bleeding domain score, at Week 104 post-BMN 270 infusion
- The change from baseline (assuming no treatment for severe hemophilia A) in Haemo-QoL-A Role functioning domain score, at Week 104 post-BMN 270 infusion

The primary analyses of Haemo-QoL-A Total score and each domain score above will be performed on the mITT population.

13.3.1 Primary Analysis Method for Secondary Efficacy Endpoints

If the hypothesis testing for the primary endpoint is significant, the secondary endpoints will be tested sequentially according to the order described above in Section 13.3.

The change from baseline in the FVIII activity at Week 104 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 ≠ 0.

Only positive changes represent efficacy.

The primary analysis will be based on the mITT population. If any subject in the mITT population has no assessment available at Week 104, 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 104, the missing value will be imputed to be 0 IU/dL at Week 104; if the subject continues on study, the missing value will be imputed to be the smaller of the median value in the subject's last visit window prior to Week 104 containing a valid observation and the median value in the subject's next visit window post Week 104 containing a valid observation. In the cases where the value of next 4-week window is unavailable (eg. Week 104 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 104 containing a valid observation.

A listing of subjects with no assessment available during Week 104 will be provided, including the imputed value and associated visit window as well as the next available FVIII activity value after Week 104 and associated visit window, if available. This is to assess potential bias in missing data imputation.

The hypotheses for change in the annualized FVIII utilization are:

H_0 (null hypothesis): Change = 0 versus H_1 (alternative hypothesis): Change ≠ 0.

Only negative changes represent efficacy. The test of annualized FVIII utilization will use a one--sample t-test with sample variance at a two-sided significance level determined by the fallback procedure. The details are described in Section 13.7.

The hypotheses for change from baseline in ABR for all bleeds are:

H_0 (null hypothesis): Change >= 0 versus H_1 (alternative hypothesis): Change < 0

The primary analysis for change from baseline in ABR for treated bleeds will be similar as that for change from baseline in ABR for all bleeds.

The change from baseline in the Haemo-Qol-A Total score at Week 104 post-BMN 270 infusion will be tested using a one-sample t-test on the mITT population using observed cases. The hypotheses are:

H_0 (null hypothesis): Change = 0 versus H_1 (alternative hypothesis): Change ≠ 0.

Only positive changes represent efficacy.

The primary analysis for Haemo-QoL-A domain scores (Physical functioning, Consequence of bleeding, Role functioning) will be the same as the Total score analyses.

13.3.2 Supportive Analysis Methods for Secondary Efficacy Endpoints

The FVIII activity level will be summarized descriptively in 4 or 6-week visit windows with missing data imputed from baseline up to the last possible visit by the data cut-off for the 2-year analysis (eg. if a subject was lost to follow-up at Week 60 and would have been followed for 104 weeks by the data cut-off, his FVIII activity levels beyond Week 60 will be imputed to be 0 IU/dL up to Week 104). The visits and visit windows are defined in Appendix 20.1 Visit Windows. Each subject's FVIII activity level in a visit window is defined as the median of the values obtained during 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 from baseline up to data cut-off. 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 at 4-week or 6-week windows (Appendix 20.1 Visit Windows) over time will be provided.

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

The maximum of each subject's FVIII activity levels (medians of the values in 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 values 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.

For long-term FVIII activity data, the overall trend will be examined. The FVIII activity levels, their changes from baseline, will be summarized descriptively at milestone timepoints defined as the end of every 6 months post-BMN 270 infusion (eg, Weeks 23-26, Weeks 49-52, Week 76 and 104 with the 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 (eg, between Weeks 23-26 and Weeks 49-52, between Weeks 49-52 and Week 76, between Week 76 and Week 104) and between Week 104 and the maximal FVIII activity by the Week 104 will also be summarized. In addition, LOESS (locally estimated scatterplot smoothing) curves of FVIII activity will be generated to show the overall trend, to compare trends between directly enrolled subjects and Study 270-902 rollover subjects, and to compare trends observed in Study 270-301 with those observed in 4E13 and 6E13 vg/kg cohorts of the Phase 2 Study 270-201.

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 104 to assess potential predictors of variability.

Total and annualized FVIII utilization (IU/kg/year) 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, Post FVIII Prophylaxis-52, Weeks 53-104, and the efficacy evaluation periods as defined in Table 13.1.1), and the annualized utilization rates will be summarized descriptively.

The analysis for the change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will be conducted using data in the efficacy evaluation periods as defined in Table 13.1.1.

Assessments of exogenous FVIII dosing and management of bleeding or peri-operative bleeding will be summarized descriptively for the mITT population.

The analyses for the change from baseline in ABR for all bleeds will be similar as the analyses for the ABR for treated bleeds.

The Haemo-QoL-A Total score will be summarized descriptively by visits. A graphical summary of mean change over time will be provided.

The analyses for Haemo-QoL-A domain scores (Physical functioning, Consequence of bleeding, Role functioning) will be the same as the Total score analyses.

13.3.3 Sensitivity Analysis Methods for Secondary Efficacy Endpoints

A one-sample t-test of the change from baseline to Week 104 in FVIII activity using observed cases will be performed as a sensitivity analysis.

The primary analysis for the change from baseline to Week 104 in FVIII activity using LOCF approach will be performed. Similarly, the primary analysis with imputing missing data at Week 104 to be 0 IU/dL will be performed.

The primary analysis for the change from baseline to Week 104 in FVIII activity 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 strategy as the primary analysis.

A mixed model for repeated measures (MMRM) approach will also be used on the observed cases on the mITT population as an alternative approach to evaluate the impact of missing data assuming missing at random. The model will include visit (every 4 weeks, from baseline to Week 104) as the only factor and will use an unstructured covariance matrix. The least squares (LS) mean change from baseline to Week 104 will be reported.

The following sensitivity analyses for the change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy will be performed:

- The primary analysis will be performed on the PP population when applicable.
- The primary analysis will be performed with baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) values calculated using the data 12-months prior to study enrollment

The Haemo-Qol-A Total score will be analyzed using an MMRM approach. The model will include visit (baseline, Week 4, Week 12, Week 26, Week 52, Week 76, Week 104) as the only factor and will use an unstructured covariance matrix. The LS mean change from baseline to Week 104 will be reported.

The analyses for Haemo-QoL-A domain scores (Physical functioning, Consequence of bleeding, Role functioning) will be the same as the Total score analyses.

13.3.4 Correlation between FVIII Activity and Bleeding Risk

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

- Using a cut-off of FVIII activity level, e.g., 40 IU/dL, each subject's data will be divided into 3 periods: baseline, from Week 5 to the first time reaching 40 IU/dL, and from the first time reaching 40 IU/dL to the end of efficacy period. For each period, the duration of the period, the number of bleeds, the ABR, and the change in ABR from baseline will be listed and summarized. ABR will also be estimated using negative binomial regression modelling number of treated bleeds vs period with period duration as the offset, repeated within subject. The analysis will be performed using various cut-off, such as 5, 15, 25, 30, 40 IU/dL.
- Based on the FVIII activity visit windows (Appendix 20.1 Visit Windows), median FVIII activity and total number of treated bleeds (defined in Section 13.2) will be calculated for each window for every subject. The total number of treated bleeds in each window will be plotted against the corresponding FVIII activity level to show the FVIII activity level around the time of bleeding. A negative binomial regression will be performed, modelling number of bleeds in each window vs. FVIII activity in the window, repeated within subject (the "repeated" term may be removed in case of convergence difficulty due to small sample size). The analysis will be done for FVIII activity measured by one--stage clotting assay and chromogenic assay separately. The same analyses will be conducted for treated joint bleeds.
- ABR will be summarized in subgroups of subjects determined by the FVIII activity levels as measured at Weeks 23-26, Weeks 49-52, Week 104, as well as by the peak FVIII activity levels.

13.3.5 Joint Analysis of ABR and Exogenous FVIII/Emicizumab Use

Per the study protocol, subjects will discontinue their regular prophylactic FVIII treatment regimen starting Week 5 post the day of BMN 270 infusion and switch to an episodic treatment schedule. In addition, subjects who experience recurrent bleeding episodes may resume their prior FVIII prophylaxis or start prophylactic emicizumab treatment. Because ABR and exogenous FVIII/emicizumab use are not independent, the following analyses will be performed to jointly assess ABR and exogenous FVIII/emicizumab use:

- Paired analysis of ABR and exogenous FVIII/emicizumab use in each of the efficacy evaluation periods defined in Section 13.1. This analysis enables the interpretation of ABR in the context of exogenous FVIII/emicizumab use.
- Summary of ABR in subgroups of subjects determined by the level of exogenous FVIII/emicizumab use:
    - Subjects who did not resume exogenous FVIII/emicizumab prophylaxis
        - Subjects with zero FVIII infusions
        - Subjects with at least one FVIII infusion
    - Subjects who resumed FVIII/emicizumab prophylaxis
        - Subjects who resumed FVIII prophylaxis
        - Subjects who resumed emicizumab prophylaxis

13.3.6 FVIII activity and ABR in immunosuppression-free periods

To investigate potential confounding effects of immunosuppressant use on the treatment effect of BMN 270, FVIII activity and ABR in immunosuppression-free periods will be assessed for study 270-902 rollover subjects. The immunosuppression-free period is defined as the efficacy evaluation period for subjects who never received immunosuppressants (i.e., systemic corticosteroids or alternative immunosuppressants) and the efficacy evaluation period after the immunosuppressant has been discontinued for subjects who did receive immunosuppressants. The efficacy evaluation period starting from the first date of immunosuppressant use through the last date of immunosuppressant use is considered as the immunosuppression period. For subjects who received and then discontinued immunosuppressants, their ABR in the immunosuppression-free period will be compared to their ABR in the immunosuppression period. This comparison will be repeated for subjects whose immunosuppression-free period is at least one year vs. less than one year. The number of subjects who were off immunosuppressants at various timepoints (e.g. 3, 6, 9, 12, 18, 24 months, etc.) and the corresponding ABR will also be summarized.

For comparison purposes, FVIII activity levels over time and ABR in the efficacy evaluation period will be summarized for subjects who never received immunosuppressants and subjects who were still on immunosuppressants at the time of the data cut-off for the analysis.

13.3.7 Impact of cessation of immunosuppressant or select concomitant medication use on FVIII expression

The impact of cessation of immunosuppressant use on FVIII expression will be evaluated in the mITT subjects who have discontinued immunosuppressant therapy before the data cut-off date for the 2-year analysis. To account for time factor, subjects will be divided into

subgroups based on their timing of immunosuppressant discontinuation (Weeks 14-26, 27-39, 40-52, et al.). Each subject's median FVIII activity level in the 4 weeks immediately after immunosuppressant discontinuation will be compared to that immediately prior. The median change in FVIII activity will be plotted against the median time to immunosuppressant discontinuation in each of the subgroups.

For comparison purposes, similar analyses will be performed to assess the natural decline of FVIII activity while subjects are on or off immunosuppressants. Changes in FVIII activity levels between 4 weeks before and 4 weeks after Week 20, 24, 28, et al. will be plotted separately for subjects who ever or never received immunosuppressant therapy.

The above analyses will be repeated for select concomitant medications (e.g., lamivudine) to assess the impact of such on FVIII expression in the mITT subjects who have discontinued them before the data cut-off date for the 2-year analysis.

13.3.8 Time to first treated bleed and restart of prophylactic treatment

Time to first treated bleed will be calculated for baseline and Post FVIII Prophylaxis periods for study 270-902 rollover subjects using the following formula:

- Baseline period: Date of first treated bleed in baseline period – Day 1 visit date in 270-902 +1
- Post FVIII Prophylaxis period: Date of first treated bleed Post FVIII prophylaxis – (BMN 270 infusion date +32 or 3 days after the end of FVIII prophylaxis, whichever is later) +1

Subjects who have zero treated bleeds in the baseline and Post FVIII Prophylaxis periods will be censored at the BMN 270 infusion date and the last visit date by data cut-off, respectively.

Time to first treated bleed will be summarized with Kaplan-Meier (KM) curves and KM quartiles (when estimable) for baseline and Post FVIII Prophylaxis periods. 2-sided 95% confidence intervals will be provided for KM quartiles (Klein and Moeschberger, 1997).

Time to first spontaneous treated bleed will be calculated and summarized in the same way as for time to first treated bleed.

Time to restart of prophylactic treatment will be calculated for the Post FVIII Prophylaxis period for all subjects:

- Date of restart of prophylactic treatment – (BMN 270 infusion date +32) +1

The definition of restart of prophylactic treatment is provided in Section 13.1. Subjects who remain on episodic treatment post-BMN 270 will be censored at the last visit date. Kaplan-

Meier (KM) curves, KM quartiles (when estimable) and associated 2-sided 95% confidence intervals will be provided for time to restart of prophylactic treatment.

Time to restart of prophylactic treatment or the first of ≥2 spontaneous treated bleeds ≤26 weeks apart (where the first spontaneous treated bleed occurred after two consecutive FVIII activity levels <5 IU/dL, based on chromogenic assay) will be calculated for the Post FVIII Prophylaxis period for all subjects. It will be calculated as the time from Week 5 (Study Day 33) or 3 days after the end of FVIII prophylaxis, whichever is later, to the restart of prophylactic treatment or the first of ≥2 spontaneous treated bleeds ≤26 weeks apart (where the first spontaneous treated bleed occurred after two consecutive FVIII activity levels <5 IU/dL, based on chromogenic assay), whichever is earlier. It will be summarized in the same way as time to restart of prophylactic treatment.

13.4 Tertiary Efficacy Endpoints

The following additional patient-reported outcomes (PROs) will be used to assess HRQoL during the study:

- Change from baseline in other domain scores of HAEMO-QoL-A (Worry, Emotional impact, Treatment concern) at Week 104 of the study post-BMN 270 infusion
- Change from baseline in the EQ-5D-5L score at Week 104 of the study post-BMN 270 infusion
- Change from baseline in the Haemophilia Activities List (HAL) score at Week 104 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 104 of the study post-BMN 270 infusion
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 104 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 tertiary endpoints (except for PROBE) will be summarized descriptively by visit up to the data cut-off. The p-value and 95% CI for the change from baseline based on two-sided t-test will be provided. The p-value is considered descriptive. PROBE will be analyzed externally through a separate statistical analysis plan.

13.4.1 Analysis Methods for Other Domain Scores of Haemo-QoL-A

The primary analyses of other Haemo-QoL-A domain scores (Worry, Emotional impact, Treatment concern) will be based on the mITT population using observed cases.

Each of the Haemo-QoL-A domain score will be analyzed using an MMRM approach. The model will include visit (baseline, Week 4, Week 12, Week 26, Week 52, Week 76, Week 104) as the only factor and will use an unstructured covariance matrix. The LS mean change from baseline to Week 104 will be reported. The domain scores will also be summarized descriptively by visits. A graphical summary of mean change over time will be provided.

13.4.2 Analysis Methods for EQ-5D-5L

The EQ-5D-5L index score (using appropriate country-based Crosswalk value sets, version 24OCT2019, referring Van Hout et al. 2012) and visual analog scale (VAS) will be analyzed for the mITT population with observed cases using the same analysis methods as Haemo-QoL-A. The number and percentage of subjects reporting each level of problem on each dimension of the EQ-5D-5L will be provided over time.

13.4.3 Analysis Methods for HAL

The HAL summary scores (upper extremity activities, basic lower extremity activities, complex lower extremity activities, overall) will be analyzed for the mITT population with observed cases using the same analysis methods as the Haemo-QoL-A total score.

The HAL domain scores (lying/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks, leisure activities and sports) will be summarized descriptively for the mITT population using observed cases.

13.4.4 Analysis Methods for WPAI+CIQ: HS

The following variables will be summarized descriptively over time for the mITT population using observed cases:

- Percent work time missed due to problems associated with hemophilia
- Percent impairment while working due to problems associated with hemophilia
- Percent overall work impairment due to problems associated with hemophilia
- Percent class time missed due to problems associated with hemophilia
- Percent impairment in the classroom due to problems associated with hemophilia
- Percent overall classroom impairment due to problems associated with hemophilia
- Percent activity impairment due to problems associated with hemophilia

13.4.5 Analysis Methods for PROBE

PROBE will be analyzed externally through a separate statistical analysis plan.

13.5 Other Efficacy Endpoints

13.5.1 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 FVIII prophylaxis, Post FVIII Prophylaxis-52, Weeks 53-104, and the efficacy evaluation periods as defined in Table 13.1.1), and the annualized 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.

13.5.2 Bleeds

The following types of bleeds will be analyzed:

- All bleeds, including both treated and non-treated
- 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, Weeks 1-end of FVIII Prophylaxis, Post FVIII Prophylaxis-52, Weeks 53-104, 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.

13.6 Examination of Efficacy by Subgroups

The following subgroup analyses may be examined for the primary and secondary efficacy endpoints:

- Age at enrollment: >=18-<30 years vs. >=30-<50 years vs. >=50 years old
- Race: Asian, Black or African American, White, Other
- Target joints at baseline: Yes vs No
- Region: Europe/Middle East, North America, South America, Africa, Australia, East Asia

Subgroup analyses based on other baseline characteristics may also be performed.

13.7 Interim Analysis and Multiplicity Adjustment

Prior to this 2-year analysis, two protocol-specified interim analyses and a 1-year analysis were planned, of which one interim analysis and the 1-year analysis were performed.

Two interim analyses were planned after approximately 16 and 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued study prior to Week 26), respectively. The concept of the interim analyses was to facilitate initiation of regulatory review of the ongoing study in the event that robust improvements (essentially normalization) in Factor VIII activity in a sufficient proportion of the subjects are observed.

The primary efficacy endpoint was subject's FVIII response status, where a subject was considered as a responder if the median FVIII activity per chromogenic assay during Weeks 23-26 post-BMN 270 infusion is ≥ 40 IU/dL. The alpha levels of 0.0002 and 0.001 were allocated to the first and second interim analysis, respectively. The second interim analysis would only occur if the result from the first interim analysis was not positive (i.e., if the pre-specified statistical significance was not achieved). A 1-year analysis was planned after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study prior to Week 52). The efficacy endpoints included change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in ABR for treated bleeds, change from baseline (assuming no treatment for severe hemophilia A) in FVIII activity per chromogenic assay at Weeks 49-52, and change from baseline (prior to BMN 270 infusion while receiving FVIII prophylaxis) in annualized FVIII utilization. These endpoints were tested sequentially using a hierarchical testing procedure at the alpha level determined by the fallback procedure (Wiens, 2005) to control the family-wise type I error rate at 0.05. Results from this analysis were intended to support regulatory submissions to EMA and other health authorities outside of FDA.

The first interim analysis was performed in May 2019 (data cut-off date: 30 April 2019) after 16 directly enrolled, HIV-negative subjects have completed the Week 26 visit. Based on the analysis results (p=0.001) and the totality of the data, the secondary interim analysis was deemed unnecessary (the test would be statistically significant at the pre-specified significance level of 0.001) and therefore never implemented. The 1-year analysis was performed in January 2021 (data cut-off date: 16 November 2020) after all subjects had been followed for 52 weeks post-BMN 270 infusion. Results from all pre-specified tests were statistically significant ($p < 0.0001$) at the alpha level of 0.0498 that was determined by the fallback procedure (SAP version 3.0, dated 17 December 2020).

- If the first interim p-value ≤0.0002, the first interim result is declared significant and the 1-year analysis is carried out at the 0.05 level.
- If the first interim p-value >0.0002, the first interim result is not declared significant and the second interim analysis is carried out at 0.001 level. If the second interim p-value ≤ 0.001, the second interim result is declared significant and the 1-year analysis is carried out at the 0.0498 level.
- If the second interim p-value >0.001, the interim results are not declared significant and the 1-year analysis is carried out at the 0.0488 level.

As specified in the 1-year analysis SAP (version 3.0, dated 17 December 2020), in the event that a 2-year final analysis is necessary, the testing procedure used in the 1-year analysis will be extended to the 2-year final analysis. That is, when all pre-specified tests (ie.

Non-inferiority test of BMN 270 vs. FVIII prophylaxis in ABR with a NI margin of 3.5, superiority test of BMN 270 vs. no treatment for severe hemophilia A in FVIII activity, superiority test of BMN 270 versus FVIII prophylaxis in FVIII utilization, superiority test of BMN 270 vs. FVIII prophylaxis in ABR) are statistically significant at the 1-year analysis, the corresponding efficacy endpoints at 2 years will be tested in the same sequence Per FDA's recommendation, the 2-year final analysis will be performed at the significance level of 0.05. The efficacy endpoints will be tested in the following hierarchical testing sequence:

1. For non-inferiority of BMN 270 versus FVIII prophylaxis in ABR (treated bleeds) with a NI margin of 3.5

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 3.5

2. For superiority of BMN 270 versus no treatment for severe hemophilia A in FVIII activity

   Null hypothesis: FVIII activity at Week 104 – baseline FVIII activity ≤ 0

3. For superiority of BMN 270 versus FVIII prophylaxis in FVIII utilization

   Null hypothesis: post-baseline FVIII utilization – baseline FVIII utilization ≥ 0

4. For superiority of BMN 270 versus FVIII prophylaxis in ABR (treated bleeds)

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 0

5. For superiority of BMN 270 versus FVIII prophylaxis in ABR (all bleeds)

   Null hypothesis: post-baseline ABR – baseline ABR ≥ 0

6. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Total score

   Null hypothesis: post-baseline total score at Week 104 – baseline total score ≥ 0

7. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Physical functioning domain score

   Null hypothesis: post-baseline physical functioning score at Week 104 – baseline physical functioning score ≥ 0

8. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Consequences of bleeding domain score

   Null hypothesis: post-baseline Consequences of bleeding score at Week 104 – baseline Consequences of bleeding score ≥ 0

9. For superiority of BMN 270 versus FVIII prophylaxis in Haemo-QoL-A Role functioning domain score

Null hypothesis: post-baseline Role functioning score at Week 104 – baseline Role functioning score ≥ 0

After the 2-year final analysis, safety and efficacy will then continue to be assessed long-term in all subjects for a total of approximately 5 years.

14 SAFETY EVALUATIONS

Safety will be assessed by adverse event reporting; clinical laboratory assessments, with particular attention to the liver tests; vital signs assessments; physical examinations; and immunogenicity. 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 Medical Dictionary for Regulatory Activities (MedDRA).

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

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

All bleeding events and suspected bleeding events, regardless of the need for exogenous FVIII therapy as treatment, should be captured in subject diaries and recorded on the designated bleeding eCRF. Bleeding events and suspected bleeding events should not be reported as adverse events, with the following exception:

- All bleeding events and suspected bleeding events which meet one or more of the criteria for being serious (refer to 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, 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 system organ class (SOC), preferred term (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
    - 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 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 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 ULN or (> ULN & > 2x baseline value), ALT> 2x baseline value, ALT> 1.5x baseline value, ALT> 1.5x baseline value or > ULN, ALT> 2x baseline value or > ULN, peak ALT level, and duration of ALT elevation will be provided. Correlation of ALT elevation to FVIII levels, as well correlation of steroid treatment to ALT elevation and FVIII levels will be presented in subjects' profile figures. Correlation of alternative immunosuppressant (AIS) treatment to ALT elevation including time to ALT elevation recovery after AIS onset will be summarized. Local ALT assessments will be analyzed similarly as the central ALT assessments, if needed. Similar analyses will be applied to other liver tests including aspartate transaminase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), bilirubin, and alkaline phosphatase (ALP), if needed.

In addition, 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.

Finally, the impact of select concomitant medication use (e.g., lamivudine) on ALT elevations will be assessed in the same manner as outlined in Section 13.3.7 in the mITT subjects who have discontinued them before the data cut-off date for the 2-year analysis.

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 Baseline, Day 4, Day 8, Week 2, Week 3, Week 4, Week 6, Week 8, Week 12, Week 16, Week 20, Week 24, Week 26, and every 4 weeks between Weeks 32-52 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 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 neutralizing antibodies (NAb) capable of interfering with FVIII activity (FVIII Inhibitors) and is determined using the Bethesda assay with Nijmegen modification. This assay is reported out in Bethesda Units (BU), with a value of <0.6 considered negative. Both assays will be performed on patient plasma samples obtained at the screening visit, and at post-baseline visits according to the protocol's schedule of events. Test results will be summarized 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 270-301 was ongoing during the COVID-19 pandemic and remained ongoing despite the disruption that occurred. The study was fully enrolled with all subjects in post-dosing follow-up when the pandemic was declared and therefore had no impact on study sample size. However, pandemic did 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. Safety and efficacy endpoint result changes relative to timing of COVID-19 pandemic will be summarized.

18 REFERENCES

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19 SUMMARY OF CHANGES TO TWO-YEAR ANALYSIS SAP

Table 19.1 provides summary of revisions across versions of SAP.

Table 19.1: Summary of Revisions

Version		Affected Section(s)	Summary of Revisions
Number	Date		
1.0	16JUL2021		Initial version
2.0	13DEC2021	Multiple	Addressed FDA SAP comments (Request for Information Oct 2021): • Added a 5th- 9th hypothesis testing for superiority in ABR for all bleeds and Haemo-QoL-A endpoints (Total Score, Physical Functioning, Consequences of Bleeding, Role Functioning) • An alpha level of 0.05 was specified for the two-year analyses • The Efficacy Evaluation Period (EEP) for the primary analysis of ABR, annualized FVIII utilizations and annualized FVIII infusions was changed from Week 5 to last visit by data cut-off to Post FVIII prophylaxis to last visit by data cut-off. • Primary estimand was clarified • Added a summary of the subjects off immunosuppressants at various timepoints and the corresponding ABR • Additional NI tests for ABR (treated bleeds) using smaller margins were removed • Clarified the purpose of pre-specifying an imputation method for missing ABR data

20 APPENDICES

20.1 Visit Windows

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

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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]
	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]
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 2 days after the end of FVIII prophylaxis]
	Post FVIII Prophylaxis - 52		Days [the later date of Day 33 or 3 days after the end of FVIII prophylaxis, 368]
	Post FVIII Prophylaxis and Beyond		≥ the later date of Day 33 or 3 days after the end of FVIII prophylaxis
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 2 days after the end of FVIII prophylaxis]
	Post FVIII Prophylaxis - 52		Days [the later date of Day 33 or 3 days after the end of FVIII prophylaxis, 368]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Post FVIII Prophylaxis and Beyond		≥ the later date of Day 33 or 3 days after the end of FVIII prophylaxis
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]
	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]

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

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	Week 17	Day 120	Days [117, 123]
	Week 18	Day 127	Days [124, 130]
	Week 19	Day 134	Days [131, 137]
	Week 20	Day 141	Days [138, 144]
	Week 21	Day 148	Days [145, 151]
	Week 22	Day 155	Days [152, 158]
	Week 23	Day 162	Days [159, 165]
	Week 24	Day 169	Days [166, 172]
	Week 25	Day 176	Days [173, 179]
	Week 26	Day 183	Days [180, 186]
	Week 27	Day 190	Days [187, 193]
	Week 28	Day 197	Days [194, 200]
	Week 29	Day 204	Days [201, 207]
	Week 30	Day 211	Days [208, 214]
	Week 31	Day 218	Days [215, 221]
	Week 32	Day 225	Days [222, 228]
	Week 33	Day 232	Days [229, 235]
	Week 34	Day 239	Days [236, 242]
	Week 35	Day 246	Days [243, 249]
	Week 36	Day 253	Days [250, 259]
	Week 38	Day 267	Days [260, 273]
	Week 40	Day 281	Days [274, 287]
	Week 42	Day 295	Days [288, 301]
	Week 44	Day 309	Days [302, 315]
	Week 46	Day 323	Days [316, 329]
	Week 48	Day 337	Days [330, 343]
	Week 50	Day 351	Days [344, 357]
	Week 52	Day 365	Days [358, 371]
	Week 56	Day 393	Days [372, 406]
	Week 60	Day 421	Days [407, 434]
	Week 64	Day 449	Days [435, 462]
	Week 68	Day 477	Days [463, 490]
	Week 72	Day 505	Days [491, 518]
	Week 76	Day 533	Days [519, 546]
	Week 80	Day 561	Days [547, 574]
	Week 84	Day 589	Days [575, 602]
	Week 88	Day 617	Days [603, 630]
	Week 92	Day 645	Days [631, 658]

Assessment	Derived Visit	Scheduled Visit Day[a]	Window[b]
	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]
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	Week 226	Day 1587	Days [1567, 1608]
	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 dosing 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 dosing.

[d] For subjects enrolled from Study 270-902, the baseline value is derived from the period between the 270-902 enrollment day and the BMN 270 infusion day. For subjects not entering from 270-902, the baseline value is derived from the period between 12 months prior to 270-301 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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Approval	PI PI, BioStatistics 10-Dec-2021 19:31:04 GMT+0000
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