CLINICAL STUDY PROTOCOL

Study Title:	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 at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions
Protocol Number:	270-302
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	2017-003573-34 IND #: 017659
Indication:	Hemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3
Sponsor's Responsible Medical Monitor:	[redacted]
Duration of Subject Participation:	Approximately 264 weeks
Dose:	4E13 vg/kg
Study Population:	Males aged 18 or older
Date of Original Protocol:	15 September 2017
Date of Amendment 1 (Global):	26 January 2018
Date of Amendment 2 (Global):	10 July 2018
Date of Amendment 3 (Global):	28 August 2018
Date of Amendment 4 (Global):	9 November 2018

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment 4

Date: 9 November 2018

RATIONALE AND SUMMARY OF CHANGES

A summary of major changes covered by Amendment 4 to the 270-302 protocol is provided below:

1. Some visits during Year 1 of the study have been designated as optional mobile nursing or lab draw-only visits.

Rationale: The number of full study visits at the site through Week 52 creates high subject and site staff burden, in terms of frequent travel to and lengthy time spent at the site by subjects and assessments deemed to no longer be mandatory performed by investigators. This amendment will reduce the number of site visits for subjects who have the option to conduct visits via a mobile nursing professional (similar to the option already available starting in Year 2 of the study). For subjects who must still go to the site for all assessments, this amendment will decrease the time they will spend on-site.

As part of this change, several minor adjustments have been made to the Schedule of Events:

- The PBMC assessment at Week 34 has been eliminated.
- The VWF-Ag assessment at Week 38 has been moved to Week 36.
- The exploratory biomarker assessment at Week 13 has been moved to Week 12.
- The urinalysis assessment at Week 38 has been moved to Week 36.
- At visits where the mobile nursing or lab draw-only option is used, physical examination and vital signs assessments will not be performed.
- At mobile nursing visits, the service will collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVII use. For lab draw-only visits, this information will be collected by site staff, by calling or emailing the subjects.

2. Development of anti-FVIII inhibitory antibodies (inhibitors) has been added as an Event of Special Interest for safety reporting purposes.

Rationale: While development of FVIII neutralizing antibodies has not yet been observed in BMN 270 clinical studies, this change is being made to ensure timely reporting to health authorities.

3. Assessment of the Direct Thrombin Activity test has been removed.

Rationale: Based on the lack of correlation observed between FVIII activity levels and Direct Thrombin Activity test results in Study 270-201, it has been determined that samples for this exploratory test will no longer be collected in Study 270-302.

4. Changes have been made to correct minor errors and for purposes of clarity and consistency.

Refer to Section 25 for a summary of revisions to Amendment 3 (dated 28 August 2018).

2 SYNOPSIS

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

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 at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

PROTOCOL NUMBER:

270-302

STUDY SITES:

Approximately 40 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 3

STUDY RATIONALE:

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation pathway. This disorder can be either inherited, due to a genetic aberrancy, or an acquired immunologic process, leading to insufficient quantities of FVIII or a dysfunctional FVIII, but all are characterized by a defective coagulation process. The clinical phenotype of HA patients generally correlates tightly with the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild-type (< 1 IU/dL), moderate disease comprises 1-5% of wild-type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA are frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved. Subjects with moderate disease can exhibit manifestations similar to those seen in patients with severe HA, resulting in a comparable bleeding phenotype.

Treatment of severe HA presently consists of intravenous injection of plasma-derived or recombinant human FVIII protein (rhFVIII) concentrates, both as prophylaxis 2-3 times per week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12 to 18 hours for most approved products) necessitates frequent infusions, and although a major advance in the treatment of HA, it remains common for severe HA patients to continue to have multiple bleeding events on prophylactic therapy (median ABR of 1-4 with prophylaxis treatment in a recently published retrospective observational study (Berntorp, 2017) and between 1-2 in 6 prospective FVIII interventional studies) and on-demand-only therapy (median ABR of 4.5-18 in a recently published retrospective study (Berntorp, 2017) and

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

between 20-60 in 6 prospective FVIII interventional studies). The consequence of multiple bleeding events is the development of debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above a 1% trough for a greater proportion of the dosing interval. However, patients with severe HA who are treated with extended half-life FVIII remain dependent on multiple infusions to maintain critical levels of FVIII activity. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and hemorrhage-free life.

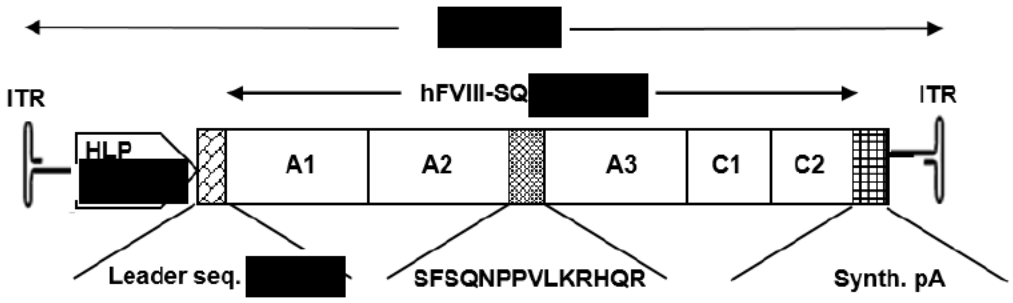
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. Hemophilia A is well-suited for a gene replacement approach because clinical manifestations are attributable to the lack of a single gene product (FVIII) that circulates in minute amounts (200 ng/ml) in the plasma. Tightly regulated control of gene expression is not essential, and even modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of hemophilia A. Thus, relatively small changes in endogenous FVIII activity can result in clinically relevant improvements in disease phenotype. Finally, the circulating FVIII response to gene transduction can be assessed using validated quantitative rather than qualitative endpoints that are easily assayed using established laboratory techniques.

Several different gene transfer strategies for FVIII replacement have been evaluated, but adeno-associated viral (AAV) vectors show the greatest promise. They have an excellent and well-defined safety profile, and can direct long-term transgene expression with tropism and promoter specificity for specific tissues, such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an ongoing gene therapy clinical trial for a related disorder, hemophilia B, has established that stable (median follow-up of 3.2 years) expression of human factor IX (hFIX) at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein infusion of AAV8-hFIX vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous hemorrhages, even when they undertook activities that previously resulted in bleeding. Thus, gene therapy treatment has resulted in a substantial improvement in their quality of life (Nathwani, 2014).

BMN 270 is an AAV5-based gene therapy vector that expresses the SQ form of hFVIII under the control of a hybrid human liver-specific promoter (Figure 1).

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Figure 1: hFVIII-SQ Vector Genome Schematic



Legend –Note that schematic is not to scale:

BMN 270 will be delivered by a single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue.

BMN 270 is being evaluated in clinical study 270-201, an ongoing first-in-human, phase 1/2 dose escalation study in subjects with severe HA designed to assess the safety and efficacy of BMN 270 at various dose levels (6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, 6E13 vg/kg). Specifically, 270-201 explores the relationship of vector dose to the augmentation of residual FVIII activity and whether these levels are sufficient to alter the clinical phenotype. Preliminary results from 270-201 have demonstrated that following gene transfer, FVIII activity above 15% (15 IU/dL) and, in many cases, within the normal range for FVIII, is achievable with a dose of 4-6E13 vg/kg with an acceptable safety profile (Pasi, 2017).

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

OBJECTIVES:

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy from Week 5 to Week 52

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

- Assess the impact of BMN 270 on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 on patient-reported outcomes (PROs) at Week 52 of the study compared to baseline

The safety objectives of the study are to:

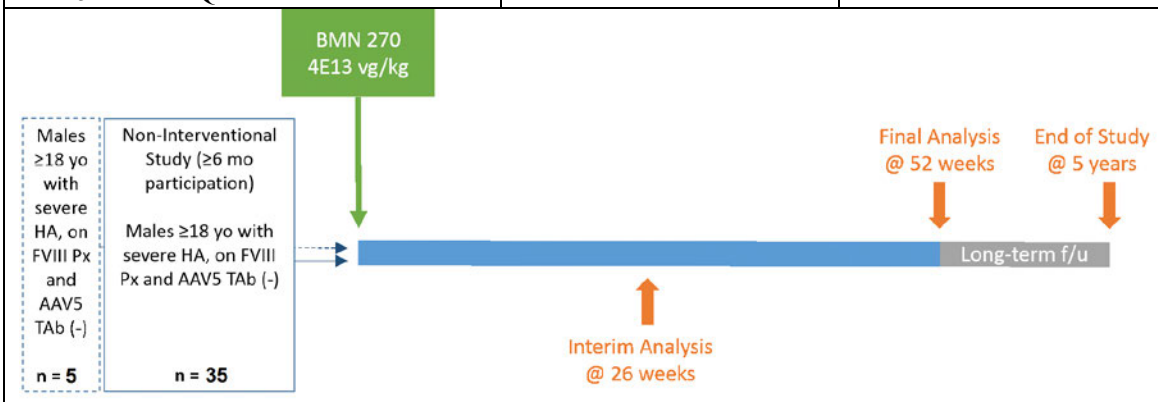
- Evaluate the safety of BMN 270 during the first 52 weeks following intravenous infusion
- Assess the long-term safety of BMN 270

STUDY DESIGN AND PLAN:

This is a Phase 3, single-arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. Subjects will be enrolled at approximately 40 sites worldwide. 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 40 adult subjects with severe HA will receive a 4E13 vg/kg dose of BMN 270 as a single intravenous infusion. Approximately 5 subjects will enroll in the study with at least 12 months of well-documented high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage, while approximately 35 subjects will 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 will be prospectively collected.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:



yo = years old, HA = hemophilia A, FVIII = factor VIII, Px = prophylaxis, AAV5 = adeno-associated virus, serotype 5, TAb = total antibody, mo = month, vg = vector genomes, kg = kilogram, f/u = follow-up.

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 will have sole access during the trial to amalgamated FVIII activity levels, FVIII usage, and bleeding data and review available safety and efficacy (eg, FVIII activity) data during the study on an ongoing basis; they may determine, based on emerging data and the risk/benefit profile, that further enrollment at 4E13 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 40 subjects, at the new BMN 270 dose level (regardless of the number of subjects previously enrolled at 4E13 vg/kg).

An interim analysis is planned after approximately 20 treated HIV-negative subjects have completed the Week 26 visit. Data will be reviewed by the DMC, based on the statistical analysis plan, and a formal recommendation will be made whether to continue the study as designed.

The final analysis for the study will be performed after all subjects have been followed for 52 weeks post-BMN 270 infusion. After the final analysis, safety and efficacy will then continue to be assessed long-term in all subjects for a total of approximately 5 years.

To avoid breakthrough bleeding, subjects will only discontinue 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.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 or inability to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes, in the judgment of the Investigator) may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Therapeutic oral corticosteroids may be initiated when a subject's ALT values are elevated, and subsequent dosage adjustments made, after consultation between the Investigator and the Medical Monitor.

Any safety signal may trigger a review of the data and possible additional immunogenicity studies or other diagnostics deemed necessary that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMCs).

NUMBER OF SUBJECTS PLANNED:

Approximately 40 subjects may enroll into the study.

DIAGNOSIS AND ALL CRITERIA FOR INCLUSION AND EXCLUSION:

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Males ≥ 18 years of age with hemophilia A and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history, at the time of signing the informed consent.
2. 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.
3. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs).
4. Willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any study-related procedures.
5. No previous documented history of a detectable FVIII inhibitor, and results from a Bethesda assay or Bethesda assay with Nijmegen modification of less than 0.6 Bethesda Units (BU) (or less than 1.0 BU for laboratories with a historical lower sensitivity cutoff for inhibitor detection of 1.0 BU) on 2 consecutive occasions at least one week apart within the past 12 months (at least one of which should be tested at the central laboratory).

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

6. Sexually active participants must agree to use an acceptable method of effective contraception, either double barrier contraception (ie, condom + diaphragm; or condom or diaphragm + spermicidal gel or foam) or their female partner either using hormonal contraceptives or having an intrauterine device. Participants must agree to contraception use for at least 12 weeks post-infusion; after 12 weeks, subjects may stop contraception use only if they have had 3 consecutive semen samples with no detectable viral vector DNA.
7. Willing to abstain from alcohol consumption for at least the first 52 weeks following BMN 270 infusion.

Patients are excluded from the study if any of the following criteria apply:

1. Detectable pre-existing antibodies to the AAV5 capsid.
2. Any evidence of active infection or any immunosuppressive disorder, including HIV infection.
3. Significant liver dysfunction with any of the following abnormal laboratory results:
   - ALT (alanine aminotransferase) > 1.25x ULN;
   - AST (aspartate aminotransferase) > 1.25x ULN;
   - GGT (gamma-glutamyltransferase) >1.25x ULN
   - Total bilirubin >1.25x ULN;
   - Alkaline phosphatase >1.25x ULN; or
   - INR (international normalized ratio) ≥ 1.4.

   Subjects whose liver laboratory assessments fall outside of these ranges may undergo repeat testing of the entire liver test panel within the same Screening window and, if eligibility criteria are met on retest, may be enrolled after confirmation by the Medical Monitor.
4. Prior liver biopsy showing significant fibrosis of 3 or 4 as rated on a scale of 0-4 on the Batts-Ludwig (Batts 1995) or METAVIR (Bedossa 1996) scoring systems, or an equivalent grade of fibrosis if an alternative scale is used.
5. Evidence of any bleeding disorder not related to hemophilia A.
6. Platelet count of < 100 x 10^9/L.
7. Creatinine ≥ 1.5 mg/dL.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

8. Liver cirrhosis of any etiology as assessed by liver ultrasound.
9. Chronic or active hepatitis B as evidenced by positive serology testing (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and hepatitis B core antibody [HBcAb]) and confirmatory HBV DNA testing. Refer to the Centers for Disease Control (CDC) table for the interpretation of serological test results in the Laboratory Manual.
10. Active Hepatitis C as evidenced by detectable HCV RNA or currently on antiviral therapy.
11. Active malignancy, except non-melanoma skin cancer.
12. History of hepatic malignancy.
13. Treatment with any Investigational Product within 30 days or 5 half-lives of the investigational product prior to the screening period. For subjects who have received a prior investigational product, all ongoing adverse events (AEs) experienced while receiving that investigational product must have resolved prior to screening for this study.
14. Any condition that, in the opinion of the Investigator or Sponsor would prevent the patient from fully complying with the requirements of the study (including possible corticosteroid treatment outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
15. Prior treatment with any vector or gene transfer agent.
16. Major surgery planned in the 52-week period following the infusion with BMN 270.
17. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
18. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study that does not interfere with the requirements of the current protocol or have the potential to impact the evaluation of efficacy and safety of BMN 270 and with prior consultation with the Medical Monitor.
19. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
20. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

INVESTIGATIONAL PRODUCT(S), DOSE, ROUTE AND REGIMEN:

Each subject will receive a single intravenous infusion of BMN 270 at 4E13 vg/kg. The volume of infusion will depend on the subject's weight.

REFERENCE THERAPY(IES), DOSE, ROUTE AND REGIMEN:

No reference therapy will be evaluated in this study.

DURATION OF TREATMENT:

BMN 270 is given as a single dose by intravenous infusion.

CRITERIA FOR EVALUATION:

Efficacy:

Primary efficacy endpoint:

- Change of the hFVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post-BMN 270 infusion from baseline. Each subject's hFVIII activity during Weeks 49-52 is defined as the median of the values obtained during this 4-week window. Values for hFVIII activity will be excluded if obtained within 72 hours since the last infusion of exogenous FVIII protein concentrates.

Secondary efficacy endpoints:

- Change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion from the baseline utilization of exogenous FVIII replacement therapy.
- Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) during Week 5 to Week 52 of the study post-BMN 270 infusion from the baseline ABR.

Tertiary efficacy endpoints:

- Change from baseline in the total score of HAEMO-QoL-A at Week 52 of the study post-BMN 270 infusion.
- Change from baseline in the EQ-5D-5L score at Week 52 of the study post-BMN 270 infusion.
- Change from baseline in the Haemophilia Activities List (HAL) score at Week 52 of the study post-BMN 270 infusion.
- Change from baseline in the Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) score at Week 52 of the study post-BMN 270 infusion.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 of the study post-BMN 270 infusion.

Safety:

The following safety outcome measurements will be assessed:

- 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, feces, saliva)
- Liver tests (LTs, including ALT, AST, GGT, total bilirubin, and alkaline phosphatase)
- Immune response to FVIII transgene product and AAV5 capsid proteins

Each subject will have comprehensive surveillance monitoring of LTs (once per week for Weeks 1-36, and then once every 2 weeks from Weeks 37-52) during Year 1. LTs will be monitored every four weeks during Year 2 and then every 6 weeks during Years 3-5 post-dose in the safety extension; the frequency and duration of LT testing may be changed based on discussion between the Medical Monitor and the Investigator, review of subject data, and/or by independent DMC feedback.

There will be a detailed assessment of cellular and humoral responses to AAV5 capsid and FVIII protein.

Pharmacodynamics:

The FVIII protein concentration and activity level as measured by a validated immunoassay and a validated FVIII activity assay, respectively, will be used for plasma profiles; FVIII protein and activity will be used to determine PD parameters.

STATISTICAL METHODS:

Sample Size

Approximately 40 subjects may be dosed in the study. The sample size for this study is 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, a sample size of 40 will provide at least 90% power to demonstrate that the change in hFVIII activity during Weeks 49-52 from baseline 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.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

For the secondary endpoints, the analyses will be performed utilizing exogenous FVIII use and bleeding episode data from the 35 subjects whose baseline data will be prospectively collected for approximately 6 months in the non-interventional study 270-902, prior to their enrollment in 270-302. An analytic sample size of 35 will provide at least 90% power to demonstrate that the change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion from baseline is less than 0, assuming an effect size of 0.6, using a one-sample t-test with a 2-sided significance level of 0.05.

An analytic sample size of 35 will also have at least 95% power to demonstrate that the change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (ABR) during Week 5 to Week 52 of the study post-BMN 270 infusion from the baseline ABR is less than 3.5 (non-inferiority margin), assuming the pre- and post-BMN 270 infusion population mean ABRs are 3.5 and 1 respectively, using a one-sample t-test with a 2-sided significance level of 0.05.

Overall, a sample size of 40 will have greater than 80% power for testing the primary and secondary efficacy endpoints hierarchically at the final analysis with a 2-sided significance level of 0.025.

Analysis Population

The intention-to-treat (ITT) population is defined as all subjects who receive BMN 270 infusion, and the modified intention-to-treat (mITT) population is defined as subjects who receive BMN 270 infusion and are HIV-negative. The mITT population will be used for the primary efficacy analysis, and the ITT population will be used for the supportive efficacy analysis. The ITT population will also be used for the safety analysis.

Analysis

For the primary efficacy endpoint at Week 52 (ie, the change in the hFVIII activity during Weeks 49-52 post-BMN 270 infusion from baseline, as measured by chromogenic substrate assay), a one-sample t-test will be used to test the null hypothesis that the change is 0 or less against the alternative hypothesis that the change is greater than 0. Descriptive summaries of the proportions of subjects whose FVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 15, 25 and 30 IU/dL, and the confidence intervals of the proportions will also be provided.

For the secondary endpoints, the analyses will be performed on subjects in the mITT population whose baseline data will be prospectively collected for approximately 6 months in the non-interventional study 270-902 prior to their enrollment in 270-302.

NAME OF COMPANY BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949 NAME OF FINISHED PRODUCT: BMN 270 NAME OF ACTIVE INGREDIENT: AAV5-hFVIII-SQ	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

For the first secondary efficacy endpoint at Week 52 (ie, the change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion from baseline), a one-sample t-test will be performed to test the null hypothesis that the change is 0 or greater against the alternative hypothesis that the change is less than 0.

For the second secondary efficacy endpoint at Week 52 (ie, the change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment during Weeks 5-52 post-BMN 270 infusion from baseline), a one-sample t-test will be performed to test for non-inferiority of BMN 270 against FVIII prophylaxis (ie, the baseline ABR calculated using subjects' data collected in 270-902) using a margin of 3.5, ie, to test the null hypothesis that the change is 3.5 or greater against the alternative hypothesis that the change is less than 3.5. If non-inferiority is demonstrated, the test for superiority of BMN 270 against FVIII prophylaxis will be performed.

The primary efficacy endpoint and secondary efficacy endpoints will be tested hierarchically at the final analysis at Week 52 according to the order described above.

An interim analysis is planned after approximately 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued participation prior to Week 26). The primary efficacy endpoint for the interim analysis involves hFVIII activity, as measured by chromogenic substrate assay, achieved post-BMN 270 infusion, as detailed in the Statistical Analysis Plan (SAP).

Adjustment for multiplicity of the interim analysis at Week 26 and the final analysis at Week 52 will be described in the SAP (regardless of the interim analysis results, the study is planned to continue upon the DMC's recommendation, and the final analysis will be performed at Week 52). At the final analysis at Week 52, the secondary efficacy endpoints will be tested hierarchically.

The secondary efficacy endpoints at the interim analysis (Week 26) will be summarized descriptively.

The tertiary endpoints will be analyzed at the interim (Week 26) and final (Week 52) analyses, irrespective of the aforementioned hierarchical testing.

Details of the interim analysis, including the control of Type I error rate, will be specified in the SAP.

Analysis of safety endpoints will be primarily descriptive. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, seriousness, and severity. Clinical laboratory test values, vital signs, vector shedding and immune response parameters will be summarized descriptively by visit.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAV	adeno-associated virus
ABR	annualized bleeding rate
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
ART	anti-retroviral therapy
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CFR	Code of Federal Regulations
CRA	clinical research associate
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
eCRF	electronic case report form
ED	exposure days
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FIH	first-in-human
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	Hemophilia A
HAL	Haemophilia Activities List
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
hFIX	human coagulation factor IX
hFVIII	human coagulation factor VIII

HIPAA	Health Insurance Portability and Accountability Act
IB	investigator brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH E6 [R2]	ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6
IEC	independent ethics committee
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MN	mobile nursing
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PEG	polyethylene glycol
PK	Pharmacokinetics
PRO	patient-reported outcome
rhFVIII	recombinant human FVIII protein
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
TGA	thrombin generation assay
ULN	upper limit of normal
vg	vector genomes
VWF:Ag	von Willebrand factor antigen
WPAI+CIQ:HS	Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific

Definition of Terms:

Investigational Product (IP):

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use" (from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 [ICH E6 (R2)]).

The terms "IP" and "study drug" may be used interchangeably in the protocol.

5 ETHICS

BioMarin Pharmaceutical Inc. (hereafter referred to as BioMarin or the Sponsor) conducts its studies according to the highest ethical and scientific standards. The following sections articulate standards to which Investigators will be held accountable, as well as matters of compliance to document adherence to such standards.

5.1 Institutional Review Board or Independent Ethics Committee

Investigators are expected to interact with Ethics Committees (ECs) promptly, as required, during the course of the study. This includes, but is not limited to, providing appropriate documentation to support study initiation and maintaining appropriate flow of safety and other information during the course of the study and for study close-out activities. BioMarin (or designee) will assist Investigators with access to timely and accurate information and with assurance of prompt resolution of any queries.

Prior to initiating the study, the Investigator will obtain written confirmation that the institutional review board (IRB) or independent ethics committee (IEC) [for Canadian protocols, Research Ethics Board (REB)] is properly constituted and compliant with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP) requirements, applicable laws and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to BioMarin or its designee. The Investigator will provide the IRB/IEC/REB with all appropriate material, including the protocol, Investigator's Brochure (IB), the Informed Consent Form (ICF) including compensation procedures, and any other written information provided to the subjects, including all ICFs translated for patients who do not speak the local language at the clinical site. The study will not be initiated and Investigational Product (IP) supplies will not be shipped to the site until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol, the ICF and all subject recruitment materials are obtained in writing by the Investigator and copies are received at BioMarin or its designee. The approval document should refer to the study by protocol title and BioMarin protocol number (if possible), identify the documents reviewed, and include the date of the review and approval. BioMarin will ensure that the appropriate reports on the progress of the study are made to the IRB/IEC/REB and BioMarin by the Investigator in accordance with applicable guidance documents and governmental regulations.

5.2 Ethical Conduct of Study

It is expected that Investigators understand and comply with the protocol. This includes, but is not limited to: establishing and meeting enrollment commitments, including providing eligible subjects for study enrollment; adhering to adverse event reporting, diagnostic, or other procedures as specified in the protocol; and assuring appropriate compliance with study treatment administration and accountability.

This study will be conducted in accordance with the following:

- European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, for studies conducted within any European country
- US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable
- ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (ICH E6) or E6(R2) (ICH E6R2) if adopted

Specifically, this study is based on adequately performed laboratory and animal experimentation and human Phase 1 study testing. The study will be conducted under a protocol reviewed and approved by an IRB/IEC/REB and will be conducted by scientifically and medically qualified persons. The potential benefits of the study are in proportion to the potential risks. The rights and welfare of the subjects will be respected and the Investigators conducting the study do not find the hazards to outweigh the potential benefits. Each subject will provide written, informed consent before any study-related tests or evaluations are performed.

5.3 Subject Information and Informed Consent

A properly written and executed informed consent form (ICF), in compliance with ICH E6 (Section 4.8), United States Code of Federal Regulations (CFR) 21 CFR §50, European Clinical Trial Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC, and other applicable local regulations, will be obtained for each subject prior to entering the subject into the study. The Investigator will prepare the ICF and provide the documents to BioMarin for approval prior to submission to the IRB/IEC/REB. BioMarin and the IRB/IEC/REB must approve the documents before they are implemented. A copy of the approved ICF, and if applicable, a copy of the approved subject information sheet and all ICFs translated to a language other than the native language of the clinical site must also be received by BioMarin or designee prior to any study-specific procedures being performed.

The Investigator will provide copies of the signed ICF to each subject and will maintain the original in the record file of the subject.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

During administration of informed consent, expectations regarding participation in the study should be made clear to subjects. Patients who are not willing and/or are not able to comply with all aspects of the study should not be encouraged to participate.

Prior to beginning the study, the Investigator at each site must provide to BioMarin or designee a fully executed and signed Statement of Investigator (SOI) form. A US Food and Drug Administration (FDA) Form FDA 1572 serves as an acceptable SOI form. If Form FDA 1572 may not be used in a particular region, the Investigator must provide a fully executed SOI on the form provided by the Sponsor. All Investigators and Sub-Investigators must be listed on Form FDA 1572 or its equivalent SOI. Financial Disclosure Forms must also be completed for all Investigators and Sub-Investigators listed on the Form FDA 1572 or SOI who will be directly involved in the treatment or evaluation of subjects in this study.

The study will be administered by and monitored by employees or representatives of BioMarin. Clinical research associates (CRAs) or trained designees will monitor each site on a periodic basis and perform verification of source documentation for each subject as well as other required review processes. BioMarin's Regulatory Affairs Department (or designee) will be responsible for the timely reporting of serious adverse events (SAEs) to appropriate regulatory authorities as required.

In multicenter studies, a Coordinating Investigator will be identified who will be responsible for study overview. The Coordinating Investigator will read the clinical study report (CSR) and confirm that it accurately describes the conduct and results of the study, to the best of his or her knowledge. The Coordinating Investigator will be chosen on the basis of active participation in the study, ability to interpret data, and willingness to review and sign the report in a specified timeframe. The identity of the Coordinating Investigator and a list of all Investigators participating in the study will be provided in the CSR.

Clinical Laboratory assessments will be performed at a nominated central laboratory. Bioanalytical samples will be sent to the appropriate specialty laboratories for testing. Refer to laboratory manual for more details.

7 INTRODUCTION

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males (Nathwani, 1992). It is caused by mutations in the factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation pathway. Clinical manifestations of severe FVIII deficiency are frequent unprovoked bleeding episodes in joints and soft tissues causing permanent disability and occasionally death mostly after brain hemorrhage. Treatment in Western countries (Berntorp, 2012) consists of intravenous injection of plasma-derived or recombinant FVIII protein concentrates at the time of a bleed to control it or prophylactically to prevent bleeding episodes. The short half-life for FVIII (~8-12 hours) necessitates frequent infusions and makes this treatment prohibitively expensive for the majority of the world's hemophilia A patients. These individuals develop debilitating arthropathy and have a substantially increased risk of death from hemorrhage in life (Stonebraker, 2010). Chemical modification or bioengineering of FVIII may improve half-life to 18-19 hours (Kaufman, 2013). However, these extended half-life FVIII variants do not eliminate the need for lifelong FVIII protein administration (Hay, 2012).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of human FVIII (hFVIII) following a single administration of vector. Hemophilia A is well-suited for this approach because its clinical manifestations are attributable to the lack of a single gene product (FVIII) that circulates in low amounts (100-200 ng/ml) in the plasma. Tightly regulated control of gene expression is not essential, and a modest increase in the level of FVIII (a plasma level of 2 ng/ml protein leads to a 1% expression) can ameliorate the severe phenotype (Srivastava, 2013); thus, the therapeutic goal for gene therapy is a modest increase in hFVIII. Finally, the consequences of gene transfer can be assessed using simple quantitative rather than qualitative endpoints that can be easily assayed in most clinical laboratories.

BMN 270 contains the cDNA for the B-domain-deleted SQ FVIII with a liver-specific HLP transcription promoter. The expression cassette is inserted between AAV2 ITRs, and this genome is packaged in the AAV5 capsid. A comprehensive review of BMN 270 is contained in the IB supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.1 Nonclinical Studies

The nonclinical program supports a single IV infusion of BMN 270, the planned clinical route of administration, for the treatment of hemophilia A in male patients. This nonclinical program took into account the guidelines and reflection papers for gene therapy medicinal

products under EMA Advanced Therapies as well as FDA guidance. The primary pharmacodynamics (PD), pharmacokinetics (PK), and toxicity of IV BMN 270 were characterized in a series of single dose studies in species that were vector permissive and responsive to the transgene including normal CD-1 mice, a B- and T-cell deficient mouse model of hemophilia A (B6;129S-*F8*^{tm1Kaz}/J x B6.129S6-*Rag2*^{tm1Fwa} N12; FVIII KO x Rag2), and normal cynomolgus and rhesus monkeys. Some PD studies evaluated additional PK, immunogenicity and toxicity endpoints.

Results of the nonclinical program to date are detailed in the IB supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.2 Previous Clinical Studies

Study BMN 270-201 is an ongoing Phase 1/2, dose-escalation study to assess the safety, tolerability, and efficacy of BMN 270 in patients with severe hemophilia A (FVIII ≤1 IU/dL). Subjects received a single BMN 270 infusion and are to be followed for safety and efficacy for up to 5 years. A total of 15 subjects have been enrolled at one of 4 dose levels (6E12, 2E13, 4E13, and 6E13 vg/kg).

A comprehensive review of safety, efficacy, and immunogenicity results from 270-201 as of the latest data cut is contained in the IB supplied by BioMarin. Investigators are to review this document prior to initiating this study.

7.3 Study Rationale

Hemophilia A (HA) is an X-linked recessive bleeding disorder that affects approximately 1 in 5,000 males. It is caused by deficiency in the activity of coagulation factor VIII (FVIII), an essential cofactor in the intrinsic coagulation pathway. This disorder can be either inherited, due to a genetic aberrancy or an acquired immunologic process, leading to insufficient quantities of FVIII or a dysfunctional FVIII, but all are characterized by a defective coagulation process. The clinical phenotype of HA patients generally correlates tightly with the level of residual expression. Severe HA is classified as FVIII activity less than 1% of wild type (< 1 IU/dL), moderate disease comprises 1-5% of wild-type activity and the mild form is 5-40% activity. The clinical manifestations of severe HA are frequent spontaneous bleeding episodes, predominantly in joints and soft tissues, with a substantially increased risk of death from hemorrhage when the brain is involved. Subjects with moderate disease can exhibit manifestations similar to those seen in patients with severe HA, resulting in a comparable bleeding phenotype.

Treatment of severe HA presently consists of intravenous injection of plasma derived or recombinant human FVIII protein (rhFVIII) concentrates both as prophylaxis 2-3 times per

week, and at the time of a bleed, to prevent or control bleeding episodes, respectively. The half-life for FVIII (12 to 18 hours for most approved products) necessitates frequent infusions, and although a major advance in the treatment of HA, it remains common for severe HA patients to continue to have multiple bleeding events on prophylactic therapy (median ABR of 1-4 with prophylaxis treatment in a recently published retrospective observational study (Berntorp, 2017) and between 1-2 in 6 prospective FVIII interventional studies) and on-demand-only therapy (median ABR of 4.5-18 in a recently published retrospective study (Berntorp, 2017) and between 20-60 in 6 prospective FVIII interventional studies). The consequence of multiple bleeding events is the development of debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc fusion proteins) improve half-life by approximately 50%, and thus, show promise in reduced dosing and maintaining activity levels above 1% trough for a greater proportion of the dosing interval. However, these extended half-life FVIII variants remain dependent on multiple infusions to maintain critical levels of FVIII activity in severe HA patients. There is therefore a strong unmet need for a fully preventive treatment of HA to give patients a FVIII level compatible with a normal and hemorrhage-free life.

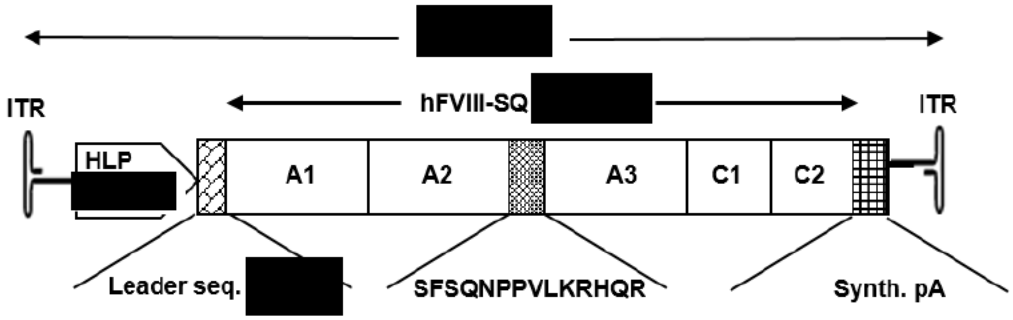
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. Hemophilia A is well-suited for a gene replacement approach because clinical manifestations are attributable to the lack of a single gene product (FVIII) that circulates in minute amounts (200 ng/ml) in the plasma. Tightly regulated control of gene expression is not essential, and even modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of the disease. Thus, relatively small changes in endogenous FVIII activity can result in clinically relevant improvements in disease phenotype. Finally, the circulating FVIII response to gene transduction can be assessed using validated quantitative rather than qualitative endpoints that are easily assayed using established laboratory techniques.

Several different gene transfer strategies for FVIII replacement have been evaluated, but adeno-associated viral (AAV) vectors show the greatest promise. They have an excellent and well-defined safety profile, and can direct long term transgene expression with tropism and promoter specificity for specific tissues such as the liver (for serotypes 2, 5 and 8 among others). Indeed, an on-going gene therapy clinical trial for a related disorder,

hemophilia B, has established that stable (median follow-up of 3.2 years) expression of human factor IX (hFIX) at levels that are sufficient for conversion of their bleeding phenotype from severe to moderate or mild is achievable following a single peripheral vein infusion of AAV8-hFIX vector. Several participants in this trial have been able to discontinue factor prophylaxis without suffering spontaneous hemorrhages, even when they undertook activities that previously resulted in bleeding. Thus, gene therapy treatment has resulted in a substantial improvement in their quality of life (Nathwani, 2014).

BMN 270 is an AAV5-based gene therapy vector that expresses the SQ form of hFVIII under the control of a hybrid human liver-specific promoter (Figure 7.3.1).

Figure 7.3.1: hFVIII-SQ Vector Genome Schematic



Legend –Note that schematic is not to scale; [redacted]

BMN 270 will be delivered by a single intravenous dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma, synthesized from vector-transduced liver tissue.

BMN 270 is currently being evaluated in clinical study 270-201, an ongoing first-in-human, phase 1/2 dose escalation study in subjects with severe HA designed to assess the safety and efficacy of BMN 270 at various dose levels (6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, 6E13 vg/kg). Specifically, 270-201 explores the relationship of vector dose to the augmentation of residual FVIII activity and whether these levels are sufficient to alter the clinical phenotype. Preliminary results from 270-201 have demonstrated that following gene transfer, FVIII activity above 15% (15 IU/dL) and, in many cases, within the normal range for FVIII, is achievable with a dose of 4-6E13 vg/kg with an acceptable safety profile (Pasi, 2017). For additional information on preliminary data in 270-201, refer to the current version of the Investigator's Brochure.

The current study is a Phase 3, single-arm, open-label study designed to assess whether, in an expanded sample, BMN 270 at a dose of 4E13 vg/kg can safely alter the clinical phenotype of hemophilia A patients with residual FVIII activity ≤ 1 IU/dL.

7.4 Summary of Overall Risks and Benefits

The majority of subjects in the ongoing 270-201 clinical study who have received 4E13 or 6E13 vg/kg doses of BMN 270 have had Grade 1 asymptomatic elevations in ALT. For most subjects, the elevations have reached only slightly above the ULN. Based on the effectiveness of transient oral corticosteroid used to suppress a presumed cytotoxic T-cell response in prior studies with hepatic transduction with AAV vectors (Mingozzi, 2013), subjects were treated with 7-32 weeks of oral corticosteroids preventatively or in response to the elevations in ALT to ensure preservation of the transduced hepatocytes. Using this approach, no sustained loss of FVIII activity has been observed in subjects with ALT elevations, consistent with maintaining a high level of hepatocyte function. Moreover, the rise in ALT levels were not accompanied by significant or lasting aberrations in other liver tests such as AST, bilirubin or albumin, indicating that extent of toxicity is limited. There has been one HIV-positive subject in the ongoing 270-302 clinical study who experienced Grade 3 asymptomatic elevations in ALT and AST, which has been attributed to an interaction between one or more of his antiretroviral therapy medications and/or unsuspected underlying hepatic disease with BMN 270. In addition, there has been one subject with Gilbert's syndrome in the ongoing 270-301 clinical study who has experienced Grade 3 asymptomatic elevations in ALT and AST. These cases have led to the exclusion of subsequent HIV-positive subjects and requirement of liver tests at Screening that are <1.25 times the upper limit of the normal range in the ongoing 270-301 and 270-302 clinical studies. Of note, two HIV-positive subjects in 270-301 and one presumed Gilbert's syndrome subject in 270-201 have received BMN 270 without experiencing any elevations in ALT to date. Overall, the literature and clinical experiences with BMN 270 thus far suggest that transient elevations in liver enzymes are expected following AAV-based gene therapy for the treatment for hemophilia B without any long-term concerns of hepatic injury (Manno, 2006); (Nathwani 2011); (George, 2016); (Miesbach, 2016), (Pasi, 2017).

At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII levels above 50 IU/dL at 52 weeks post-infusion. Similarly, subjects who received 4E13 vg/kg have achieved FVIII levels within or approaching the normal range. Subjects in both cohorts also reported markedly decreased bleeding compared with pre-study rates and the ability to discontinue prophylactic FVIII infusions. Subjects at all dose levels continue to be followed.

As with any infused biological product, there is a potential risk of acute, systemic hypersensitivity reactions (including anaphylaxis) with BMN 270. No hypersensitivity reactions were observed during dosing of BMN 270 in the 270-201 clinical study, although one SAE of pyrexia was reported approximately 16 hours after the infusion in a subject in the 4E13 vg/kg cohort. The subject was treated with acetaminophen, and the fever resolved within 48 hours (see Investigator's Brochure for full details). Infusion-related reactions, including allergic reaction, maculopapular rash, and presyncope, have been reported from ongoing, actively dosing clinical studies of BMN 270. All of the infusion-related reactions were effectively managed clinically and resolved without any clinical sequelae. Refer to the Investigator's Brochure for additional details.

The current data available for BMN 270 does not yet permit adequate assessment of the benefit:risk profile of this investigational drug. Given the monitoring measures in place in the clinical protocol(s) to minimize the risk to subjects participating in the existing studies, the identified risks are justified by the anticipated benefits that may be afforded to subjects. Each subject in 270-302 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LT will be addressed according to the guidelines set forth in the protocol. Safety will be assessed by adverse event reporting and clinical laboratory assessments.

For additional information on findings in 270-201, refer to the current version of the Investigator's Brochure.

8 STUDY OBJECTIVES

The primary efficacy objective of the study is to:

- Assess the efficacy of BMN 270 defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 following intravenous infusion of BMN 270

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 on usage of exogenous FVIII replacement therapy from Week 5 to Week 52
- Assess the impact of BMN 270 on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 on patient-reported outcomes (PROs) at Week 52 of the study compared to baseline

The safety objectives of the study are to:

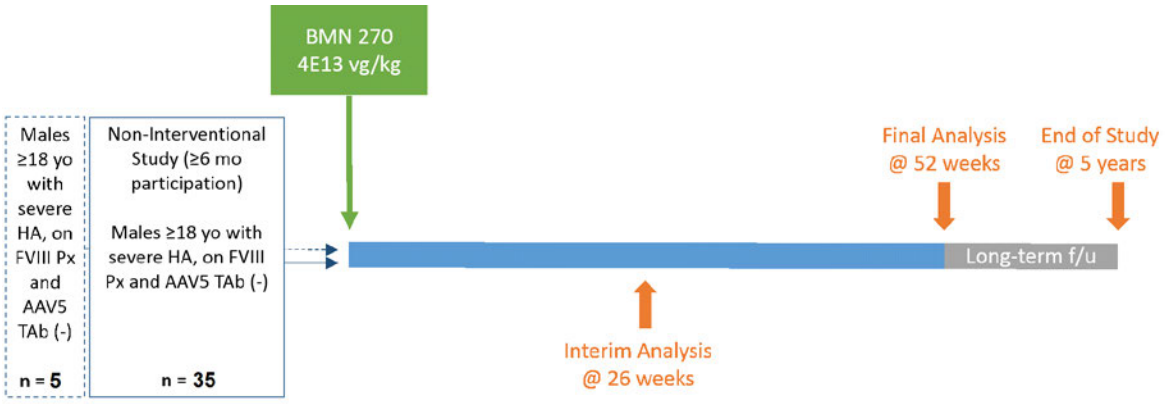
- Evaluate the safety of BMN 270 during the first 52 weeks following intravenous infusion
- Assess the long-term safety of BMN 270

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3, single-arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL treated continuously with prophylactic exogenous FVIII for a minimum of one year prior to enrollment. Subjects will be enrolled at approximately 40 sites worldwide. 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 40 adult subjects with severe HA will receive a 4E13 vg/kg dose of BMN 270 as a single intravenous infusion. Approximately 5 subjects will enroll in the study with at least 12 months of well-documented high-quality historical data concerning previous bleeding episodes and exogenous FVIII usage, while approximately 35 subjects will 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 prior to gene therapy will be prospectively collected.



yo = years old, HA = hemophilia A, FVIII = factor VIII, Px = prophylaxis, AAV5 = adeno-associated virus, serotype 5, TAb = total antibody, mo = month, vg = vector genomes, kg = kilogram, f/u = follow-up.

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 will have sole access during the trial to amalgamated FVIII activity levels, FVIII usage, and bleeding data and will review available safety and efficacy (eg, FVIII activity) data during the study on an ongoing basis; they may determine, based on emerging data and the risk/benefit profile, that further enrollment at 4E13 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 40 subjects, at the new BMN 270 dose level (regardless of the number of subjects previously enrolled at 4E13 vg/kg).

An interim analysis is planned after approximately 20 treated HIV-negative subjects have completed the Week 26 visit.

The final analysis for the study will be performed after all subjects have been followed for 52 weeks post-BMN 270 infusion. After the final analysis, safety and efficacy will then continue to be assessed long-term in all subjects for a total of approximately 5 years.

To avoid breakthrough bleeding, subjects will only discontinue 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.

As the relationship between activity assay results of the BMN 270 gene product and bleeding remains to be established, Investigators should strive to minimize bias by avoiding consideration of FVIII activity levels by themselves or subjects in the reporting of bleeding episodes and FVIII usage.

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

Subjects who do not respond to BMN 270 treatment [redacted] ay, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Therapeutic oral corticosteroids may be initiated when a subject's ALT values are elevated, and subsequent dosage adjustments made, after consultation between the Investigator and the Medical Monitor. Management of ALT elevations is discussed in more detail in Section 9.7.8.3.

Any safety signal may trigger a review of the data and possible additional immunogenicity studies or other diagnostics deemed necessary that include an assessment of cellular immune responses using collected peripheral blood mononuclear cells (PBMCs).

Schedules of assessments for the Screening and Infusion period (Table 9.1.1), Post-Infusion follow-up periods (Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5), and during the use of oral corticosteroids (Table 9.1.6) are presented below.

Table 9.1.1: Schedule of Events – Screening and Infusion

Assessment	Prior to BMN 270 Infusion			BMN 270 Infusion Visit (Day 1)[k]
	Screening* (Day -28 to Day -1)	Smart Rescreening[i] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[h]	
Informed consent	X			
Demographics (age, sex, race, ethnicity)	X			
Medical History	X			
Physical Examination[a]	X		X	X
Height and Weight	X			
Vital Signs	X	X	X	X
Assessment of Adverse Events and Concomitant Medications	X	X	X	X
Documentation of bleeding episodes and FVIII usage for previous 12 months (by either subject or clinical information)	X	X	X	
Distribution of subject diaries and training in their use[l]	X			
Electrocardiogram	X			
Liver Ultrasound	X			
hFVIII Assays[b]	X	X[j]	X	
AAV5 TAb Assays[c]	X	X	X	X
AAV5 TI Assay			X	
Screen for Hepatitis B, Hepatitis C, HIV[d]	X			
Blood chemistry, hematology, and coagulation tests[e]	X	X	X	
Fasting lipid panel (blood triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol)				X
Urine Tests[e]	X	X	X	
Liver Tests[e]	X	X	X	
PBMC collection (for baseline determination of AAV5 and FVIII specific cellular immunity)			X	

Assessment	Prior to BMN 270 Infusion			BMN 270 Infusion Visit (Day 1)[k]
	Screening* (Day -28 to Day -1)	Smart Rescreening[i] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[h]	
Von Willebrand Factor Antigen (VWF:Ag)			X	
TGA Assay[g]			X	
PCR of vector DNA in blood, saliva, urine, semen, and stools			X	X
Biomarker testing[f]	X			
Exploratory biomarker assessments[g]			X	X
Haemo-QOL-A assessment			X	
EQ-5D-5L			X	
HAL			X	
WPAI+CIQ:HS			X	
PROBE			X	
BMN 270 Infusion				X
Hypersensitivity blood assessments[m]				X[m]

* Screening assessments should be performed within 28 days of BMN 270 infusion (and must be performed within 42 days prior to BMN 270 infusion).

[a] Complete physical examination should be done at Screening. Brief physical examination may be done at Baseline and at the BMN 270 Infusion Visit.

[b] Includes baseline FVIII activity (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), coagulation exploratory assay, hFVIII inhibitor level (Bethesda assay with Nijmegen modification), hFVIII total antibody titer, and hFVIII protein assay. Baseline activity should be assessed at trough (at least >72 hours after last dose of replacement FVIII therapy, or 5x the known half-life of the FVIII concentrates administered).

[c] Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given. Screening, Smart Re-screening, and Infusion Day samples will be tested in an AAV5 TAb pre-screening assay specifically developed for enrollment purposes. Baseline and all post-dose samples will be tested in a different AAV5 TAb post-dose immunogenicity monitoring assay

[d] Patients with documented negative results within the last 30 days do not need to be retested. Hepatitis B screening should include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb).

[e] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study).

[f] Includes HLA genotyping and FVIII genotyping.

[g] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay, and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[h] Should the screening visit occur within 30 days of the drug infusion, physical examination, blood chemistry, LTs, hematology, urine tests, and coagulation tests do not need to be repeated at Baseline.

[i] Smart rescreening should only be performed if a patient has been determined to be eligible for the study and is unable to complete the Baseline assessments and Infusion prior to the closing of the original Screening window. Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.

[j] Only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification) assay must be done at smart rescreening.

[k] With the exception of the collection of samples for PCR vector DNA analysis, assessments on the day of infusion must be performed prior to the infusion. Subjects will fast for at least 8 hours prior to pre-infusion laboratory sampling on the day of the infusion visit. On the day of the BMN 270 Infusion, vital signs will be monitored prior to the infusion, during the infusion every 15 minutes (± 5 minutes), and following the infusion hourly (± 5 minutes) for at least 8 hours during the subject's stay in the clinic. Shedding samples for PCR of vector DNA (blood, saliva, urine, semen, stool) should be collected between 2 and 24 hours after the infusion has been completed.

[l] Diaries should be distributed to subjects who have consented to participate in the study and who have been determined to meet all study eligibility criteria.

[m] In case of hypersensitivity or adverse drug reaction, safety assessment, including physical examination and vital signs, will be done and additional blood samples will be collected [redacted] In-patient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up (Week 1-16)

Assessment	Follow-Up After BMN 270 Infusion – Weeks*																
	Week 1																
	D4	D8	2	3	4	5[g]	6	7[g]	8	9[g]	10	11[g]	12	13[g]	14	15[g]	16
Study Day*	4	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113
Physical examination[a]		X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X
Weight[a]					X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X
Blood chemistry, hematology, and coagulation tests[b]			X		X						X						X
Urine Tests[b]													X				
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII antibody titer					X				X				X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	X	X	X	X	X		X		X				X				X
Exploratory biomarker assessments[e]							X						X				X
Haemo-QOL-A assessment					X								X				
EQ-5D-5L					X								X				
HAL					X								X				

Assessment	Follow-Up After BMN 270 Infusion – Weeks*																
	Week 1																
	D4	D8	2	3	4	5[g]	6	7[g]	8	9[g]	10	11[g]	12	13[g]	14	15[g]	16
Study Day[*]	4	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113
WPAI+CIQ:HS					X								X				
PROBE					X								X				
AAV5 TAb Assay									X								X
AAV5 TI Assay									X								X
Testing for reactivation of hepatitis B and hepatitis C																	X[f]
PBMC collection (for determination of AAV5 and FVIII specific immunity)			X		X		X		X		X		X		X		X
VWF:Ag													X				

[*] Visit windows are ± 48 hours (and include the Day 4 visit).

[a] Brief physical examination should be done at all weekly visits.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests (LTs). LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN and > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN. Subjects with ALT ≥1.5x ULN or > ULN and > 2x baseline value during the study and either an alternative etiology considered or for further evaluation of the lab abnormality may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the Investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, coagulation exploratory assay, and hFVIII protein assay. If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII ≥ 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A D-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism.

[d] Collection for each matrix to occur until at least 3 consecutive negative results are obtained. Collection and testing of semen samples must continue at least through Week 12, even if 3 consecutive negative results in that compartment have already been recorded.

[e] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[f] Testing for reactivation of hepatitis B and hepatitis C at Week 16, for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry, should be performed only in subjects who have not received therapeutic oral corticosteroids prior to Week 16; subjects who have received therapeutic oral corticosteroids will have hepatitis B and hepatitis C testing at the time points indicated in Table 9.1.6.

[g] The scheduled visits at Week 5, Week 7, Week 9, Week 11, Week 13, and Week 15 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.

Table 9.1.3: Schedule of Events – Post-Infusion Follow-Up (Week 17-32)

Assessment	Follow-Up After BMN 270 Infusion – Weeks*															
	17[f]	**18**	**19[f]**	**20**	**21[f]**	**22**	**23[f]**	**24**	**25[f]**	**26**	**27[f]**	**28**	**29[f]**	**30[f]**	**31[f]**	**32**
Study Day*	120	127	134	141	148	155	162	169	176	183	190	197	204	211	218	225
Physical examination[a]	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X[f]	X[f]	X
Weight[a]				X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X	X[f]	X[f]	X[f]	X
Blood chemistry, hematology, and coagulation tests[b]						X				X						X
Urine Tests[b]										X						
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII antibody titer				X				X		X						X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]				X				X		X						X
Exploratory biomarker assessments[e]				X				X		X						X
Haemo-QOL-A assessment										X						
EQ-5D-5L										X						

Assessment	Follow-Up After BMN 270 Infusion – Weeks*															
	17[f]	**18**	**19[f]**	**20**	**21[f]**	**22**	**23[f]**	**24**	**25[f]**	**26**	**27[f]**	**28**	**29[f]**	**30[f]**	**31[f]**	**32**
Study Day*	120	127	134	141	148	155	162	169	176	183	190	197	204	211	218	225
HAL										X						
WPAI+CIQ:HS										X						
PROBE										X						
AAV5 TAb Assay								X								X
AAV5 TI Assay								X								X
PBMC collection (for determination of AAV5 and FVIII specific cellular immunity)		X		X		X		X		X		X		X		X
VWF:Ag										X						
TGA Assay[c]				X				X		X						X

* Visit windows are ± 48 hours.

[a] Brief physical examination should be done at all weekly visits except Week 26, where a complete physical examination should be performed. Weight should be recorded at Week 20 and every 4 weeks.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are ≥ 1.5x ULN or > ULN and > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN. Subjects with ALT ≥ 1.5x ULN or > ULN and > 2x baseline value during the study and either an alternative etiology considered or for further evaluation of the lab abnormality may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the Investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, coagulation exploratory assay, and hFVIII protein. If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII ≥ 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between

the Medical Monitor and the Investigator. A D-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism.

[d] Collection for each matrix to occur until at least 3 consecutive negative results are obtained.

[e] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[f] The scheduled visits at Week 17, Week 19, Week 21, Week 23, Week 25, Week 27, Week 29, Week 30, and Week 31 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.

Table 9.1.4: Schedule of Events – Post-Infusion Follow-Up (Week 33 – Week 52)

Assessment	Year 1 – Weeks*											
	33[e]	**34[e]**	**35[e]**	**36**	**38[e]**	**40**	**42[e]**	**44**	**46[e]**	**48**	**50[e]**	**52**
Study Day[*]	232	239	246	253	267	281	295	309	323	337	351	365
Physical examination[a]	X[e]	X[e]	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]	X
Weight[a]				X		X		X		X		X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X[e]	X[e]	X[e]	X	X[e]	X	X[e]	X	X[e]	X	X[e]	X
Blood chemistry, hematology, and coagulation tests[b]				X				X				X
Urine Tests[b]				X								X
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X
AAV5 TAb Assay				X								X
AAV5 TI Assay				X								X
FVIII antibody titer				X				X				X
Exploratory biomarker assessments[d]				X		X		X		X		X
PBMC Collection (for determination of FVIII and Capsid specific cellular immunity)				X				X				X
VWF:Ag				X								X
TGA Assay[d]				X		X		X		X		X
PCR of vector DNA in blood, saliva, urine, semen, and stools				X		X		X		X		X
Haemo-QOL-A assessment												X
EQ-5D-5L												X
HAL												X
WPAI+CIQ:HS												X

Assessment	Year 1 – Weeks*											
	33[e]	34[e]	35[e]	36	38[e]	40	42[e]	44	46[e]	48	50[e]	52
PROBE												X

* Visit windows are ± 48 hours through Week 36, then ±1 week until Week 52.

[a] Complete physical examination should be performed at Week 52; brief physical exam may be performed at other study visits. Weight should be recorded at Week 36 and every 4 weeks through Week 52.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN and > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN. Subjects with ALT ≥1.5x ULN or > ULN and > 2x baseline value during the study and either an alternative etiology considered or for further evaluation of the lab abnormality may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the Investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, coagulation exploratory assay, and hFVIII protein assay. If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII ≥ 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A D-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism.

[d] Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[e] The scheduled visits at Week 33, Week 34, Week 35, Week 38, Week 42, Week 46, and Week 50 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.

Table 9.1.5: Schedule of Events – Post-Infusion Follow-Up (Year 2 – Year 5)

Assessment	Years 2-5*	Year 2*	Years 3-5*	End of Year Visit				ETV
				Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
Physical examination[a]	X[a]			X[a]				X
Weight[a]	X[a]			X[a]				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	X				X
Vital Signs	X			X				X
Blood chemistry, hematology, and coagulation tests[b]	X[b]			X[b]				X
Urine Tests[b]	X[b]			X[b]				X
Liver Tests[b]	X	X	X	X				X
FVIII assays[c]	X	X	X	X				X
AAV5 TAb Assay	X			X				X
AAV5 TI Assay	X			X				X
FVIII antibody titer	X			X				X
Exploratory biomarker assessments[e]	X			X				X
PBMC Collection (for determination of FVIII and Capsid specific cellular immunity)	X			X				X
VWF:Ag	X			X				X
TGA Assay[e]	X			X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	(X)[d]	(X)[d]	(X)[d]	(X)[d]				(X)[d]
Haemo-QOL-A assessment	X[f]			X[f]				X
EQ-5D-5L	X[f]			X[f]				X
HAL	X[f]			X[f]				X
WPAI+CIQ:HS	X[f]			X[f]				X

Assessment	Years 2-5*	Year 2*	Years 3-5*	End of Year Visit				ETV
				Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
PROBE	X[f]			X[f]				X

* Visit windows are ± 2 weeks for visits in Years 2-5. At applicable sites, the Q4W (during Year 2) and Q6W (during Years 3-5) assessments may be conducted by a trained mobile nursing (MN) professional at the subject's home or another suitable location, if the subject has given written informed consent to participate in mobile nursing visits. Q12W and End of Year visits during Years 2-5 cannot be done by a MN professional and must be done at the study site.

[a] Complete physical examination should be performed at the End of Year visits; brief physical exam may be performed at other study visits. Weight should be recorded at the second Q12W visit each year and at every End of Year visit during Years 2-5.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. LTs may be monitored more or less frequently (and in particular when ALT values are ≥ 1.5x ULN or > ULN and > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN. Subjects with ALT ≥ 1.5x ULN or > ULN and > 2x baseline value during the study and either an alternative etiology considered or for further evaluation of the lab abnormality may undergo additional evaluations (eg, imaging studies including MRI or ultrasound, additional blood tests, and/or liver biopsy) at the discretion of the Investigator. Additional testing of FVIII and LTs during any study week may be performed if: (1) the ALT has increased to above ULN or increased by > 10 U/L from prior assessment; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level; or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If FVIII levels and/or ALT values are stable over the course of several weeks, assessment of FVIII activity and ALT levels may be adjusted based on discussion between the Medical Monitor and the Investigator. During Years 2-5 of the Post-Infusion Follow-Up period, urine tests and blood, chemistry, and coagulation tests should be performed at the second Q12W visit each year and at every End of Year visit.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level, coagulation exploratory assay, and hFVIII protein assay. If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; the 72-hour wash-out period is only intended for subjects who have achieved FVIII ≥ 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy. If FVIII levels are elevated or stable over the course of several weeks, assessment of FVIII activity may be adjusted based on discussion between the Medical Monitor and the Investigator. A D-dimer may be considered under circumstances in which FVIII activity levels are above the normal physiological range and/or if there is a concern for a venous thromboembolism. If a subject tests positive in the Bethesda assay (with Nijmegen modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.

[d] Sample testing during Long-Term Follow-Up is not required if at least 3 consecutive samples were negative during the Post-Infusion Follow-Up period. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of 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).

[e] Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[f] PRO assessments during Years 2-5 of Long-Term Follow-up should be performed at the second Q12W visit each year and at every End of Year visit.

[g] Subjects who meet the definition of treatment failure to BMN 270 therapy after Week 52 may omit the Q4W and Q6W visits during Years 2-5, and must attend only the Q12W and End of Year visits. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in all fluids must still provide samples Q4W (during Year 2) or Q6W (during Years 3-5) until vector shedding has been cleared, either by reporting to the site to provide samples or by providing those samples to a MN professional.

Table 9.1.6: Schedule of Events – Therapeutic Corticosteroids for ALT Elevations

	Steroid Treatment Period[b]								Post-Steroid Period[c]				
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8[b]**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 13**
Therapeutic corticosteroids (dose in mg/day) [a]	60 mg	60 mg	40 mg	40 mg	40 mg	30 mg	20 mg	10 mg					
FVIII activity testing									X	X	X	X	
Liver tests									X	X	X	X	
Hepatitis B testing[d]						X			X				X
HCV Viral Load[d]						X			X				X

[a] Therapeutic oral corticosteroids may be initiated according to the parameters set out in Section 9.4.8.2.

[b] Following initiation or completion of steroid regimen, if a recurrence of ALT values ≥ 1.5x ULN or > ULN and > 2x baseline value is reported, steroid management decisions will based on discussions between the Investigator and Medical Monitor. Modification of the steroid regimen may take into consideration possible confounders for the ALT elevation, relationship between increases in ALT and FVIII activity, ALT/FVIII levels post steroid initiation, and adverse events related to steroid dosing. Guidance for tapering oral corticosteroid dosing can be found in Section 9.4.8.2.

[c] After discontinuation of oral corticosteroids, weekly labs for ALT and FVIII levels will be measured once a week for 4 weeks to ensure stability in values. If these assessments are already being done as part of normal study follow-up, they do not need to be duplicated.

[d] Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-302 is designed to be a Phase 3, single-arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL previously treated with prophylactic exogenous FVIII. Hemophilia A patients who provide written informed consent, meet the entry criteria definition of residual FVIII activity, have well-documented historical data for the previous 12 months concerning exogenous FVIII usage and bleeding episodes, and do not have antibodies to AAV5 will be eligible to enroll in the study.

Approximately 40 subjects will be enrolled at the 4E13 vg/kg BMN 270 dose. Subjects will be followed for 52 weeks post-BMN 270 infusion during which safety and efficacy assessments will be taken. After the final analysis at 52 weeks post-infusion, safety and efficacy will then continue to be assessed long-term for approximately a total of 5 years. During enrollment, the DMC will review available safety and efficacy data on an ongoing basis and may decide to recommend dosing subjects at a different dose level (not to exceed 6E13 vg/kg) based on emerging data from 270-302 and their overall benefit:risk assessment.

Study 270-302 is a self-controlled study. Parameters for each subject will be compared to a pre-treatment assessment of safety (liver function) and efficacy (number of bleeds, use of FVIII replacement therapy).

9.3 Selection of Study Population

Approximately 40 adult hemophilia A patients with residual FVIII levels ≤ 1 IU/dL may enroll into the study.

Additional criteria for participation in the study are provided in Section 9.3.1 and Section 9.3.2.

9.3.1 Inclusion Criteria

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

1. Males ≥ 18 years of age with hemophilia A and residual FVIII levels ≤ 1 IU/dL as evidenced by medical history, at the time of signing the informed consent.
2. 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.
3. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs).

4. Willing and able to provide written, signed informed consent after the nature of the study has been explained and prior to any study-related procedures.
5. No previous documented history of a detectable FVIII inhibitor, and results from a Bethesda assay or Bethesda assay with Nijmegen modification of less than 0.6 Bethesda Units (BU) (or less than 1.0 BU for laboratories with a historical lower sensitivity cutoff for inhibitor detection of 1.0 BU) on 2 consecutive occasions at least one week apart within the past 12 months (at least one of which should be tested at the central laboratory).
6. Sexually active participants must agree to use an acceptable method of effective contraception, either double-barrier contraception (ie, condom + diaphragm; or condom or diaphragm + spermicidal gel or foam) or their female partner either using hormonal contraceptives or having an intrauterine device. Participants must agree to contraception use for at least 12 weeks post-infusion; after 12 weeks, subjects may stop contraception use only if they have had 3 consecutive semen samples with no detectable viral vector DNA.
7. Willing to abstain from alcohol consumption for at least the first 52 weeks following BMN 270 infusion.

9.3.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Detectable pre-existing antibodies to the AAV5 capsid.
2. Any evidence of active infection or any immunosuppressive disorder, including HIV infection.
3. Significant liver dysfunction with any of the following abnormal laboratory results:
   - ALT (alanine aminotransferase) > 1.25x ULN;
   - AST (aspartate aminotransferase) > 1.25x ULN;
   - GGT (gamma-glutamyltransferase) > 1.25x ULN;
   - Total bilirubin > 1.25x ULN;
   - Alkaline phosphatase > 1.25x ULN; or
   - INR (international normalized ratio) ≥ 1.4.

   Subjects whose liver laboratory assessments fall outside of these ranges may undergo repeat testing of the entire liver test panel within the same Screening window and, if eligibility criteria are met on retest, may be enrolled after confirmation by the Medical Monitor.

4. Prior liver biopsy showing significant fibrosis of 3 or 4 as rated on a scale of 0-4 on the Batts-Ludwig (Batts 1995) or METAVIR (Bedossa 1996) scoring systems, or an equivalent grade of fibrosis if an alternative scale is used.
5. Evidence of any bleeding disorder not related to hemophilia A.
6. Platelet count of $< 100 \times 10^9$/L.
7. Creatinine ≥ 1.5 mg/dL.
8. Liver cirrhosis of any etiology as assessed by liver ultrasound.
9. Chronic or active hepatitis B as evidenced by positive serology testing (HBsAg, HBsAb, and HBcAb) and confirmatory HBV DNA testing. Refer to the Centers for Disease Control (CDC) table for the interpretation of serological test results in the Laboratory Manual.
10. Active Hepatitis C as evidenced by detectable HCV RNA or currently on antiviral therapy.
11. Active malignancy, except non-melanoma skin cancer.
12. History of hepatic malignancy.
13. Treatment with any Investigational Product within 30 days or 5 half-lives of the investigational product prior to the screening period. For subjects who have received a prior investigational product, all ongoing adverse events (AEs) experienced while receiving that investigational product must have resolved prior to screening for this study.
14. Any condition that, in the opinion of the Investigator or Sponsor would prevent the patient from fully complying with the requirements of the study (including possible corticosteroid treatment outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
15. Prior treatment with any vector or gene transfer agent.
16. Major surgery planned in the 52-week period following the infusion with BMN 270.
17. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
18. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study that does not interfere with the requirements of the current protocol or have the potential to impact the evaluation of efficacy and safety of BMN 270 and with prior consultation with the Medical Monitor.
19. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
20. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

9.3.3 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in the study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. Such subjects will always be asked about the reason(s) for withdrawal. The Investigator will discuss with the subject appropriate procedures for withdrawal from the study. The Investigator should ask the subject's consent to perform the procedures listed under the early termination visit. Should a subject withdraw from the study, all efforts will be made to complete and report the observations as thoroughly as possible up to the date of the withdrawal.

A subject's participation in the study may be discontinued at any time at the discretion of BioMarin or of the Investigator and in accordance with his/her clinical judgment. When possible, the tests and evaluations listed for the termination visit should be carried out and every effort will be made to gather follow-up safety data if possible.

BioMarin must be notified of all subject withdrawals as soon as possible. BioMarin also reserves the right to discontinue the study at any time for either clinical or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Reasons for which the Investigator or BioMarin may withdraw a subject from the study include, but are not limited to, the following:

- Subject requires medication or medical procedure prohibited by the protocol
- Subject does not adhere to study requirements specified in the protocol
- Subject was erroneously enrolled into the study or does not meet entry criteria and not yet been dosed with BMN 270; subjects who do not meet entry criteria but who erroneously receive BMN 270 should remain in the study for safety monitoring
- Subject is lost to follow-up

If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone, a certified letter should be sent to the subject requesting contact with the Investigator. This information should be recorded in the study records.

The Investigator or designee must explain to each subject, before enrollment into the study, that for evaluation of study results, the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC/REB. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected

health information per country-specific regulations, such as the Health Insurance Portability and Accountability Act (HIPAA) in the US, from each subject. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

9.3.3.1 Study Safety Evaluation Criteria

If any of the following events occur in a subject in the study who has received BMN 270 infusion, an urgent evaluation by the DMC will be required and further enrollment into the trial will be temporarily put on hold if recommended by the DMC per Section 9.1.

1. Liver dysfunction (criteria do not apply to ALT elevations with an extra-hepatic etiology):
    - ALT > 5x ULN, for more than 2 weeks
    - ALT > 3x ULN **and** (total bilirubin >2x ULN **or** INR >1.5)
    - ALT > 3x ULN with signs and symptoms of liver dysfunction
2. The occurrence of Grade 4 or Grade 5 adverse events assessed as related to study drug (events of liver dysfunction are defined above).
3. The occurrence of an AE of hepatic failure.
4. The detection of high-titer neutralizing antibodies (>5 BU) to hFVIII following BMN 270 infusion in two subjects.
5. The occurrence of any cancer (except non-melanoma skin cancer) at any point after BMN 270 infusion.
6. The occurrence of a thromboembolic event with FVIII activity > 150 IU/dL in one subject.

If any of the following events occurs in a subject in the study who has received BMN 270 infusion, an urgent evaluation by the DMC will be required. Further enrollment into the trial will continue while DMC evaluation is ongoing, unless deemed otherwise by the DMC:

1. The detection of high-titer neutralizing antibodies (>5 BU) to hFVIII following BMN 270 infusion in one subject.
2. Occurrence of a thromboembolic event in one subject.

9.3.4 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages. In legal jurisdictions where use of initials is not permitted, a substitute identifier will be used.

Subjects who withdraw from the study after receiving BMN 270 will not be replaced.

9.3.5 Duration of Subject Participation

The duration of participation for each subject will be approximately 264 weeks. This includes 4 weeks of screening, 1 day of BMN 270 infusion, 52 weeks of Post-Infusion Follow-Up, and 208 weeks of Long-Term Follow-Up.

9.4 Treatments

9.4.1 Treatments Administered

BioMarin and/or its designee will provide the study site with a supply of IP sufficient for the completion of the study. BioMarin is responsible for shipping study drug to clinical sites.

9.4.2 Identity of Investigational Product

9.4.2.1 Product Characteristics and Labeling

[redacted]

The study drug is labelled according to the particulars approved by the relevant regulatory agencies.

9.4.3 Storage

At the study site, all IP must be stored under the conditions specified in the Pharmacy Manual in a secure area accessible only to the designated pharmacists and clinical site personnel. All IP must be stored and inventoried and the inventories must be carefully and accurately documented according to applicable state, federal and local regulations, ICH GCP, and study procedures.

9.4.4 Directions for Administration

On the day of infusion, the subject will come to the infusion site, where a physical examination will be performed by the Investigator or designee. If the subject is found to have an active acute illness at the time of planned infusion, then the infusion should be deferred until the illness has resolved; screening procedures may require repetition if outside the specified window. An IV catheter or butterfly needle will be inserted into a suitable peripheral vein (eg, the median cubital vein) and flushed with saline. FVIII replacement

therapy will not be given since venipuncture is a minimally invasive procedure in these individuals under ordinary conditions.

[redacted] Vital signs (pulse, blood pressure, respiration rate and temperature) should be monitored at 15 minute (±5 minutes) intervals throughout the time period of the infusion.

As with any infused biological product, there is a potential risk of acute, systemic hypersensitivity reactions (including anaphylaxis) with BMN 270. Dosing will be administered at a qualified infusion site, with appropriate resuscitation equipment and medication available and easily accessible.

Clinical staff administering BMN 270 should be trained appropriately in recognizing and managing the signs and symptoms associated with potential hypersensitivity, anaphylactic, and anaphylactoid reactions. Additionally, the Investigator should be familiar with Sampson's criteria for defining anaphylaxis (Sampson, 2006; Appendix 1).

Should symptoms of potential hypersensitivity occur, the infusion may be slowed or halted at the Investigator's discretion, with consideration of the subject's clinical condition. If the infusion is halted, it should only be restarted if the Investigator considers it safe and appropriate to do so. Antihistamines, anti-pyretic, and/or corticosteroid administration is permitted prior to restarting an interrupted infusion by an infusion-related reaction. At the restart, the infusion rate may be adjusted [redacted] with careful monitoring of the subject.

In case of hypersensitivity or adverse drug reaction, safety assessment, including physical examination and vital signs, will be done and additional blood samples will be collected [redacted]

[redacted] In-patient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

Following completion of the infusion, vital signs will be monitored hourly (±5 minutes). If the vital signs are stable the catheter will be removed 8 hours after the infusion. Hemostasis at the puncture site will be established by applying pressure according to standard protocol for infusing FVIII concentrates. Subjects will remain in the clinic for at least 8 hours to observe for any immediate toxicity of the procedure; in-patient observation can be extended beyond 8 hours if needed per Investigator discretion, or the subject may transfer to a separate facility based on the evaluation and judgment of the Principal Investigator after consultation with the Medical Monitor.

Prior to discharging subjects from the clinic, the Investigator or designee should instruct subjects how to recognize signs and symptoms of potential (delayed) hypersensitivity reactions and anaphylaxis, and to contact a medical practitioner or seek emergency care in case of such an event.

9.4.5 Method of Assigning Subjects to Treatment Groups

Subjects who meet all eligibility criteria (refer to Section 9.3.1 and Section 9.3.2) may be enrolled into the study. Approval by the Medical Monitor will be required prior to enrollment of each study subject. Upon their enrollment into the study, subjects will be assigned a unique subject number.

Approximately 40 subjects will be enrolled at 4E13 vg/kg.

9.4.6 Selection of Dose Used in the Study

Data from an ongoing first in human study (Clinical Study 270-201) indicates that following single escalated doses of BMN 270 (6E12, 2E13, 4E13, 6E13 vg/kg), dose-related increases in FVIII activity were observed, with concurrent improvements in bleeding episodes and exogenous FVIII utilization, particularly at the 4E13 and 6E13 vg/kg dose levels. At all dose levels, BMN 270 is considered to be well-tolerated with mild increases in ALT as the most common adverse event. Please refer to the IB for detailed efficacy and safety data.

In order to further evaluate the dose-response relationship of BMN 270, subjects will be enrolled at a dose of 4E13 vg/kg. This dose is expected to be safe and effective based on clinical experience to date in 270-201. The DMC will review emerging safety and efficacy data and may recommend that a different dose (not to exceed 6E13 vg/kg) be administered. In such a case, up to 40 additional subjects may be enrolled at the new dose.

9.4.7 Blinding

This is an open-label study.

9.4.8 Prior and Concomitant Medications

All prescription and over-the-counter medications (including dietary and herbal supplements) taken by a subject for 30 days before Screening will be recorded on the designated eCRF. The Investigator may prescribe additional medications, deemed necessary to provide adequate prophylactic or supportive care, during the study, as long as the prescribed medication is not prohibited by the protocol. In the event of an emergency, any needed medications may be prescribed without prior approval, but the Medical Monitor must be notified of the use of any contraindicated medications immediately thereafter. Any concomitant medications added or discontinued during the study should be recorded on the eCRF. Medications should, whenever possible, not be recorded in the electronic database with a frequency of PRN.

The following medications are prohibited starting 30 days before Screening and through the end of the study, and the Sponsor must be notified if a subject receives any of these during the study:

- Any investigational therapy
- Systemic immunosuppressive agents, except for corticosteroids
- Emicizumab
- Fitusiran
- Concizumab
- Efavirenz
- Lamivudine

The following medications should be avoided, starting 30 days prior to and for at least 52 weeks after BMN 270 infusion and minimized throughout the remaining duration of the study.

- Alcohol
- Herbal and natural remedies and dietary supplements
- Medications which may be hepatotoxic

Vaccines should also be avoided during this period, but in particular during the first 26 weeks unless clinically indicated.

The following medications should be avoided during oral corticosteroid therapy:

- Vaccines
- NSAIDs

9.4.8.1 Concomitant Hemophilia Treatments

Subjects on prophylactic FVIII therapy will discontinue their regular treatment regimen starting 4 weeks after the day of infusion and switch to an “on-demand” schedule. FVIII replacement therapy can always be taken as needed by the subject for treatment of an acute bleeding episode; the subject must carefully record his treatment and bleeding episodes in his diary. Prophylactic FVIII use can be used on a case-by-case basis and in consultation with the Medical Monitor to prevent bleeding in extenuating circumstances (eg, peri-operative).

In addition, information on FVIII usage and bleeding episodes by medical history must be well-documented and available and will be collected from subjects for the 12-month period immediately preceding study enrollment. Further information on the details that should be provided as part of the subject’s well-documented medical and FVIII usage history are provided in the On Site File Binder.

In order to enable rigorous comparisons of pre-study versus on-study FVIII usage and bleeding episodes, the Medical Monitor will review each screened patient’s prior bleed and hemophilia medication logs to determine if they are of "high-quality". Elements that will be assessed to judge the quality of such historical data may include, but are not limited to, the following:

- Date, type (eg, joint, muscle, other), location of bleeds
- Date, name, dose (calculated in IU/kg), and reason for use (eg, usual prophylaxis, one-time prophylaxis, treatment for bleed, surgery) of hemophilia medications.

9.4.8.2 Therapeutic Glucocorticoid Treatment of Elevated Hepatic Transaminases

Therapeutic oral corticosteroids (prednisone or converted equivalent) should be initiated when either of the following occurs post-BMN 270 infusion in any subject and after consultation with the Medical Monitor:

- ALT ≥ 1.5x ULN or ALT > ULN & > 2x baseline value in 2 consecutive assessments within 72 hours and alternative etiologies have been ruled out, or ALT ≥ 3x ULN in 2 consecutive assessments within 48 hours (refer to Table 9.7.8.3.2)
    - Whenever possible, a confirmatory lab draw for ALT should be performed, along with FVIII activity, prior to initiating oral corticosteroids.

- Corticosteroids may be delayed if elevations in ALT are clearly not related to BMN 270 (eg, elevated in ALT with concurrent increase in CPK due to intensive exercise)

The prescribed regimen for therapeutic oral corticosteroids is detailed in Table 9.1.6. Changes to the corticosteroid regimen should be made as follows:

Table 9.4.8.2.1: Adjustments to Corticosteroid Regimen

Tapering Corticosteroid Dose	Subject has been receiving oral corticosteroids <3 weeks	Corticosteroids may be discontinued **if**: • ALT < 1.5x ULN or ALT ≤ ULN & ≤ 2x baseline value; and • FVIII levels > 20 IU/dL and within 10% of the pre-decline FVIII levels; and • There is no concern for adrenal insufficiency post-withdrawal
	Subject has been receiving oral corticosteroids ≥3 weeks	Corticosteroids may be tapered by 10 mg weekly **if**: • ALT < 1.5x ULN or ALT ≤ ULN & ≤ 2x baseline value; and • FVIII levels > 20 IU/dL and within 10% of the pre-decline FVIII levels; and • There is no concern for adrenal insufficiency post-withdrawal
Increasing Corticosteroid Dose	If ALT level is increasing or FVIII level is decreasing while on oral corticosteroids, any increases in oral corticosteroid dosing should be made only upon consultation with the Medical Monitor	

For any scenarios that are not accounted for in the above table, a discussion should take place between the Investigator and Medical Monitor regarding corticosteroid dose adjustments.

After discontinuation of oral corticosteroids, labs for ALT and FVIII levels will be measured once a week for 4 weeks to ensure stability in values.

Following initiation or completion of therapeutic oral corticosteroids, if ALT elevation ≥1.5x ULN or ALT ≥ ULN & ≥ 2x baseline value is reported, corticosteroid management decisions will be based on discussions between the Investigator and Medical Monitor. Modification of the corticosteroid regimen may take into consideration possible confounders for the ALT elevation and impact on FVIII expression.

Management and monitoring of reactions to corticosteroids should be determined by the Investigator's clinical judgment in consultation with the Sponsor's Medical Monitor. This includes the contraindicated use of NSAIDs during corticosteroid treatment and specific monitoring not already covered by the schedule of events. The use of COX-2 inhibitors, while not contraindicated during corticosteroid treatment, should be limited, if possible. Practical management to prevent complications related to oral corticosteroid therapy may be undertaken at the discretion of the Investigator (eg, evaluation of glucose intolerance,

hyperlipidemia etc.). Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of oral corticosteroid treatment and then 1 week and 13 weeks after the completion of oral corticosteroid treatment in subjects with a history of hepatitis B or hepatitis C. All adverse events (including any adverse events suspected to be caused by or related to corticosteroid use) should be reported as outlined in Section 10 of the protocol.

9.4.8.3 Monitoring of HIV-Positive Subjects

HIV-positive subjects who have previously enrolled in 270-302 should continue anti-retroviral therapy (ART) as prescribed and follow routine monitoring of CD4 count and viral load (US Dept Health Human Services, 2014). No alterations in the monitoring are indicated for enrolled immunocompetent HIV-positive subjects who receive corticosteroids as part of their enrollment in 270-302.

9.4.9 Treatment Compliance

Study drug will be administered to subjects at the study site and/or the dosing facility by a qualified health care professional. The quantity dispensed, returned, used, lost, etc. must be recorded on a dispensing log. Sites will be instructed to return or destroy all used and unused study drug containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP(s) received and IP lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the study monitor (on-site CRA) has confirmed the accountability data, if allowed by local SOPs.

9.5.1 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials (or must be referenced in their institution SOPs).

Unused study drug may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The monitor must account for all study drug in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to BioMarin or designee and retained in the Investigator study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to BioMarin upon request. The return of

study drug or study drug materials must be accounted for on a Study Drug Return Form provided by BioMarin.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures. For additional information, please refer to the Pharmacy Manual.

9.6 Dietary or Other Protocol Restrictions

There are no dietary or other protocol restrictions for this study. Alcohol should be avoided for the first 52 weeks of the study, and particularly within 48 hours prior to lab work.

Subjects should be advised to abstain from any blood or sperm donation after BMN 270 infusion, until there is no further evidence of vector shedding from PCR analysis of samples.

9.7 Safety and Efficacy Variables

9.7.1 Safety and Efficacy Measurements Assessed

The Schedule of Events (Table 9.1.1 through Table 9.1.5) describes the timing of required evaluations.

9.7.2 Primary Efficacy Variables

9.7.2.1 FVIII Activity

The primary efficacy variable is change of the hFVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post-BMN 270 infusion from baseline. Each subject's hFVIII activity during Weeks 49-52 is defined as the median of the values obtained during this 4-week window. Values for FVIII activity will be excluded if obtained within 72 hours since the last infusion of exogenous FVIII protein concentrates.

If a subject has used FVIII within 72 hours of a measurement day, all efforts should be made to obtain FVIII activity measurements when a 72-hour interval without FVIII use is achieved; The 72-hour wash-out period is only intended for subjects who have achieved FVIII $\geq$ 5 IU/dL at 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy.

In the event of an FVIII activity level decline during the study:

- If FVIII activity has declined at least 20% from the peak but less than 35% and has declined for at least 2 consecutive assessments, FVIII activity and LTs should be repeated every 7 days until FVIII activity is stable or increasing

- If FVIII activity has declined >35% from the peak and has declined for at least 2 consecutive assessments, FVIII activity and LTs should be repeated every 72 hours until FVIII activity is stable or increasing

Note that fluctuations in FVIII activity are common, and if no clear trend indicating a decline in FVIII activity is observed, then this additional testing may be deferred (upon consultation between the Investigator and the Medical Monitor) until either a more clear trend of decline has been demonstrated or until the FVIII activity levels stabilize or increase.

Subjects who do not respond to BMN 270 treatment [redacted] may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

Details on collecting FVIII activity samples are included in the Laboratory Manual.

9.7.3 Secondary Efficacy Variables

9.7.3.1 Factor VIII Replacement Therapy/Bleeding Episodes

Secondary efficacy variables are:

- Change of the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Week 5 to Week 52 post BMN 270 infusion from the baseline utilization of exogenous FVIII replacement therapy.
- Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment during Week 5 to Week 52 of the study post BMN 270 infusion from the baseline ABR.

Subjects must have high quality 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. During the study, subjects will be asked at each study visit to report the use of factor replacement therapy and the number of bleeding episodes since the previous visit. This information will be captured on the subject's diary or other subject records.

Subjects are strongly encouraged to immediately consult Investigator for guidance regarding exogenous FVIII administration for suspected bleeds or bleeding episodes within the first 30 days post BMN 270 infusion.

In subjects who experience recurrent bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis.

9.7.4 Tertiary Efficacy Variables

9.7.4.1 Patient-Reported Outcomes (PRO)

The Haemo-QoL-A questionnaire is a validated hemophilia-specific health-related quality of life questionnaire for adults (Rentz, 2008). It consists of 41 questions covering six domains (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns). Items are answered on a 6-point Likert-type scale, ranging from 0 (None of the time) to 5 (All of the time). Higher scores mean better health-related quality of life or less impairment for a particular subscale (Haemo-QoL Study Group, 2017). Details regarding the Haemo-QoL-A assessment will be included in the On Site File Binder.

The EQ-5D-5L instrument is a self-reported questionnaire designed to measure general health status (The EuroQol Group, 1990) (Brooks, 1996). The EQ-5D-5L is composed of 2-parts: a descriptive system that assesses 5 levels of perceived problems (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) in 5 dimensions and the EQ visual analogue scale (EQ VAS) assessment for overall health. A sample copy of the EQ-5D-5L and additional information are provided in the On Site File Binder.

The Haemophilia Activities List (HAL) measures the impact of hemophilia on self-perceived functional abilities in adults (Van Genderen, 2006). The instrument consists of multiple domains including lying/sitting/kneeling/standing, leg and arm function, use of transportation, self-care, household tasks, and leisure activities where subjects are asked to rate their level of difficulty with activities of daily living on a 6-point Likert-type scale from 1 (Impossible) to 6 (Never). For some items, subjects are given the choice to answer 'Not applicable'. A sample copy of the HAL and additional information are provided in the On Site File Binder.

The Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) instrument is designed to measure the effect of disease symptom severity on work productivity and classroom productivity (if applicable) (Recht, 2014). The WPAI+CIQ:HS questionnaire yields scores related to work/classroom absenteeism, reduced on-the-job effectiveness, overall work/classroom impairment, and activity impairment. WPAI+CIQ:HS outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity (Reilly, 2002). A sample copy of the WPAI+CIQ:HS and additional information are provided in the On Site File Binder.

The Patient Reported Outcomes, Burdens, and Experiences (PROBE) questionnaire is designed to investigate and directly probe patient perspectives on outcomes they deem relevant to their life and care. PROBE aims to develop a new global tool to enhance the direct patient-voice in health care decision-making (Chai-Adisaksopha, 2017). A sample copy of the PROBE questionnaire and additional information are provided in the On Site File Binder.

9.7.5 Immunogenicity

Immunogenicity assays will be performed on plasma and PBMCs. The assays will include detection of anti-AAV5 capsid and anti-FVIII total antibodies, as well as determination of neutralizing antibodies against FVIII (FVIII inhibitors) and against the AAV5 capsid (Transduction Inhibitors, TI). FVIII Inhibitors will be assessed using the Bethesda assay with Nijmegen modification. Any abnormality of the liver parameters will lead to a retrospective immunogenicity assessment to evaluate FVIII- and capsid-specific cellular immunogenicity. FVIII- and capsid-specific cellular immunity will be assessed by stimulated cytokine secretion using an ELISpot assay performed on collected PBMCs.

9.7.6 Pharmacodynamics

The FVIII protein concentration and activity level as measured by a validated immunoassay and by a validated FVIII activity assay, respectively, will be used for plasma profiles; FVIII protein and activity will be used to determine PD parameters.

9.7.7 Exploratory Assessments

Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A.

All biomarker samples collected in this study may be used for exploratory biomarker research, including evaluation of additional biomarkers not specifically listed in the protocol. In addition, samples collected for other purposes in this study may be used for exploratory research once testing for the primary purpose has been completed.

9.7.8 Safety Variables

Safety in this study will be determined from evaluation of AEs, clinical laboratory assessments with a particular attention to the liver function, vital signs assessments, physical examinations, and immunogenicity.

9.7.8.1 Adverse Events

The determination, evaluation and reporting of AEs will be performed as outlined in Section 10.

9.7.8.2 Clinical Laboratory Assessments

The scheduled clinical laboratory tests are listed in Table 9.7.8.2.1. Refer to the On Site File Binder for instructions on obtaining and shipping samples.

Any abnormal test results determined to be clinically significant by the Investigator should be repeated (at the Investigator's discretion) until: (1) the cause of the abnormality is determined; (2) the value returns to baseline or to within normal limits; or (3) the Investigator determines that the abnormal value is no longer clinically significant.

All abnormal clinical laboratory results should be initialed and dated by an Investigator, along with a comment regarding whether or not the result is clinically significant. Each clinically significant laboratory result should be recorded as an adverse event.

The diagnosis, if known, associated with abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE eCRF.

Table 9.7.8.2.1: Clinical Laboratory Tests

Blood Chemistry	Hematology	Urine Tests	Coagulation Screen including:
Albumin	Hemoglobin	Appearance	APTT
BUN	Hematocrit	Color	PT/INR
Calcium	WBC count	pH	TT
Chloride	RBC count	Specific gravity	
Total cholesterol	Platelet count	Ketones	
CPK	Differential cell count	Protein	
Creatinine	RBC indices (MCV and MCH)	Glucose	
CRP	ABO blood typing*	Bilirubin	
Glucose		Nitrite	
Phosphorus		Urobilinogen	
Potassium		Hemoglobin	
Total protein			
Sodium			
Uric Acid			

BUN, blood urea nitrogen; CPK, creatinine phosphokinase; CRP, C-reactive protein; PT, prothrombin time; APTT, activated partial thromboplastin time; RBC, red blood cell; WBC, white blood cell; TT, thrombin time; INR, international normalized ratio; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin.

*ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study).

In addition to scheduled clinical laboratory assessments, a fasting blood lipid panel (including triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) will be assessed at the BMN 270 infusion visit. Subjects will fast for at least 8 hours prior to pre-infusion laboratory sampling on the day of the infusion visit.

In case of hypersensitivity or adverse drug reaction, safety assessment, including physical examination and vital signs, will be done and additional blood samples will be collected

[redacted]

[redacted] Exploratory biomarker plasma samples collected at Baseline and at post-infusion study visits may also be used to assess the magnitude of biomarker changes.

During Years 2-5, at applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location, such as their school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be allowed for the Q4W (during Year 2) and Q6W (during Years 3-5) visits; the Q12W visits and End of Year visits during Years 2-5 will not be performed by an MN professional but will be done at the study site.

MN visits may also be available during Year 1 at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 30, 31, 33, 35, 38, 42, 46, and 50 (as indicated in the Schedule of Events).

9.7.8.3 Liver and Hepatitis Testing

Subjects will be screened for evidence of previous or active hepatitis B or hepatitis C infection at Screening; hepatitis B screening should include HBsAg, HBsAb, and HBcAb. Subjects with documented results showing an absence of active hepatitis B or hepatitis C infection (as measured by positive surface antigen for hepatitis B or positive RNA testing for hepatitis C) 30 days prior to providing signed informed consent do not need to repeat those tests during the screening period.

Evidence of ongoing hepatitis B or hepatitis C infection is exclusionary. Subjects with a history of hepatitis B or hepatitis C infection prior to study entry will be tested for hepatitis B and hepatitis C reactivation at Week 16. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received as part of their medical history assessment at Screening.

Subjects with a previous history of hepatitis B or hepatitis C who receive therapeutic oral corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.6.

A liver ultrasound and liver tests (LTs) during Screening will identify any significant hepatic dysfunction.

Liver tests will be monitored on a regular basis; at each time point, the following LTs should be assessed:

Table 9.7.8.3.1: Liver Tests

Liver Tests (LTs)			
Alkaline Phosphatase	AST (SGOT)	Total Bilirubin	LDH
ALT (SGPT)	Direct Bilirubin	GGT	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase

Elevated ALT levels (above the upper limit of normal range) should be evaluated according to the following plan:

Table 9.7.8.3.2: Evaluation of ALT Elevations

ALT Level	Work-Up
Above ULN and <1.5x ULN	• Continue to monitor LTs and FVIII per protocol (repeat within 7 days if next protocol scheduled visit is >7 days from the time of the reported ALT elevation) • Consider evaluation to rule out alternative etiology (eg, concomitant medications, viral or autoimmune hepatitis, alcohol use, recreational drug use, special diets, strenuous exercise, prior and/or concurrent illnesses, exposure to environmental and/or industrial chemicals, etc.) (refer to Table 9.7.8.3.3) • If ALT is > ULN & > 2x baseline in 2 consecutive assessments within 72 hours and alternative etiologies have been ruled out, start oral corticosteroids upon consultation with the Medical Monitor (refer to Section 9.4.8.2).
1.5 - <3x ULN	• Repeat LTs and FVIII within 72 hours • Continue to monitor LTs weekly until ALT is stable or improving • Evaluate and rule out alternative etiologies (as above) • Consult with Medical Monitor • If ALT is ≥ 1.5x ULN in 2 consecutive assessments within 72 hours and alternative etiologies have been ruled out, start oral corticosteroids (refer to Section 9.4.8.2)
≥3x ULN	• Consult with Medical Monitor • Evaluate and rule out alternative etiologies (as above) • Repeat LTs and FVIII within 48 hours, and continue with monitoring of LTs at least twice weekly for as long as the subject's ALT remains ≥ 3x ULN • If ≥3x ULN in 2 consecutive assessments within 48 hours, start oral corticosteroids (refer to Section 9.4.8.2) • Obtain other possibly relevant laboratory evaluations (albumin, PT/INR, CRP, etc.) • Obtain complete blood count with differential to assess for eosinophilia • Obtain PBMC to evaluate potential immune response (prior to starting oral corticosteroids) • If no improvement in 14 days, consider gastroenterology and/or hepatology consult, abdominal workup, imaging (including MRI or ultrasound), and/or liver biopsy as appropriate

When ruling out alternative viral or autoimmune hepatitis as part of the elevated ALT workup, the following tests should be performed:

Table 9.7.8.3.3: Viral and Autoimmune Hepatitis Testing

Viral Hepatitis Workup Testing	Autoimmune Hepatitis Workup Testing
Hepatitis A	Smooth muscle antibody
Hepatitis B	Mitochondrial antibody
Hepatitis C	Liver/kidney microsomal antibodies
Hepatitis E	Antinuclear antibody (ANA) HEP-2
Cytomegalovirus (CMV)	
Epstein-Barr virus (EBV)	
Herpes simplex virus (HSV) 1 & 2	

9.7.8.4 HIV Testing

HIV testing will be performed at Screening. Subjects with documented negative results within the last 30 days prior to screening do not need to be retested.

9.7.8.5 Vital Signs, Physical Examinations and Other Observations Related to Safety

Vital signs will include seated systolic and diastolic blood pressure, heart rate, respiration rate, and temperature. Any clinically significant change in vital signs will be recorded as an AE.

Systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, and temperature will be assessed at Screening, Baseline, and at the beginning of each visit during the Post-Infusion Follow-Up and Long-Term Follow-Up periods. On the day of the BMN 270 Infusion, vital signs will be monitored prior to infusion, during the infusion every 15 minutes (± 5 minutes), following the infusion hourly (± 5 minutes) for at least 8 hours during the subject's stay in the clinic. Any abnormal vital sign assessments should be repeated, and both values should be recorded in the eCRF.

A complete physical examination is necessary during Screening/Baseline, at Week 26 and 52 and every 52 weeks thereafter; at other visits, brief physical examinations may be performed at the discretion of the Investigator based on the subject's clinical condition. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses. During Year 1, at visits where the MN services are used or shortened lab draw-only visits are conducted at the sites, the physical examination and vital signs assessments indicated in the Schedule of Events will not be performed.

A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems.

A brief physical examination will include general appearance, cardiovascular, dermatologic, respiratory, gastrointestinal, musculoskeletal, and neurologic assessments.

Height will be recorded at Screening only. Weight will be recorded at Screening and then every 4 weeks thereafter through Week 52, and at the second Q12W visit each year and at every End of Year visit during Years 2-5.

9.7.8.6 Vector Shedding

During the Post-Infusion Follow-Up period, subjects will undergo testing of various bodily samples to look for evidence of vector shedding for possible viral transmission. Bodily fluids will be tested by polymerase chain reaction (PCR). Fluids tested will include:

- Blood
- Saliva
- Semen
- Urine
- Stool

Vector shedding will also be extensively studied in the present clinical trial, at the time points indicated in Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5. Testing will continue until at least 3 consecutive negative results are obtained. 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) and every 6 weeks (during Years 3-5) until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor). Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule (refer to Section 12.7) but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared. Such subjects may provide samples on the designated study visit dates either at the sites or through use of a MN professional.

Samples may be fractionated prior to shedding analysis in order to better characterize the presence, structure, and location of vector DNA and/or vector capsid within each matrix. If needed, the fractionation may be performed with samples collected specifically for shedding

analysis (saliva, blood, semen, urine, feces). Alternatively, the vector DNA characterization during shedding analysis may utilize already fractionated exploratory samples obtained from the above biofluids, such as exploratory plasma samples, exploratory PBMC samples, and red blood cells recovered during PBMC/plasma isolations.

Fractionation of semen to collect purified sperm separately from non-sperm cells may be performed in parallel at any visit where semen samples are collected. The shedding analysis of a fractionated semen sample will only be performed if vector DNA was detected in the whole semen sample for the same visit. Fractionation of semen during shedding analysis may be stopped if purified sperm tested positive for vector DNA on at least three visits, or if purified sperm tested negative for vector DNA on at least three consecutive visits.

Contraception use may need to be extended beyond 26 weeks in individual subjects based on observed vector shedding in semen. After 26 weeks, subjects may stop contraception use only if they have had 3 consecutive negative semen samples (upon consultation between the Investigator and Medical Monitor).

Details for sample collection and storage are provided in the Laboratory Manual.

10 REPORTING ADVERSE EVENTS

10.1 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs; measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-defined events of special interest that are deemed critical to the safety evaluation of the study drug.

10.1.1 Adverse Events

For this protocol, an adverse event (AE) is any untoward medical occurrence in a subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Events not meeting the AE definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.1.1.1 Bleeding and Suspected Bleeding Events

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 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 required exogenous FVIII as treatment).

10.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- *Note: Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.*
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. If the investigational product preparation, infusion, and post-infusion observation period require transfer to an inpatient setting for completion, in the absence of an AE, this will not be considered an SAE (refer to Section 10.4.1.7).

  Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization, the event is serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect in the child or fetus of a subject exposed to IP prior to conception or during pregnancy

- Is an important medical event or reaction – that, based on medical judgment, may jeopardize the subject or require medical/surgical intervention to prevent one of the other outcomes listed above (eg, anaphylaxis)

10.2.1 Events of Special Interest (EOSI)

The following EOSI need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, severity or causality:

- Elevation of ALT ≥1.5x ULN or ALT > ULN & >2x baseline value, regardless of whether that elevation triggers an initiation or modification of oral corticosteroid treatment
- Thromboembolic event
- Systemic hypersensitivity, anaphylactic, or anaphylactoid reactions (refer to Appendix 1)
- Development of anti-FVIII inhibitory antibodies (inhibitors)

10.3 Methods and Timing for Capturing and Assessing Safety Parameters

10.3.1 Adverse Event Reporting Period

The study AE reporting period is as follows:

- After informed consent but prior to initiation of study drug, only SAEs associated with any protocol-imposed interventions will be collected; AEs occurring during this time period should be recorded on the Medical History eCRF.
- After informed consent is obtained and following infusion of study drug, the reporting period for all non-serious AEs and SAEs begins and continues for approximately 5 years or until study discontinuation/termination, whichever is longer.

The criteria for determining, and the reporting of SAEs is provided in Section 10.2.

10.3.2 Eliciting Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences. The Investigator will record all relevant AE/SAE/EOSI information in the subject's medical record and AE Case Report Form (eCRF).

10.3.3 Assessment of Seriousness, Severity, and Causality

The Investigator responsible for the care of the subject or medically qualified designee will assess AEs for severity, relationship to study drug, and seriousness (refer to Section 10.2 for SAE definitions). These assessments must be made by a study clinician with the training and

authority to make a diagnosis (eg, MD/DO, physician's assistant, nurse practitioner, or DDS).

10.3.3.1 Seriousness

The Investigator will assess if an AE should be classified as "serious" based on the seriousness criteria enumerated in Section 10.2. Seriousness serves as a guide for defining regulatory reporting obligations.

10.3.3.2 Severity

Severity (as in mild, moderate, or severe headache) is not equivalent to seriousness, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The Investigator will determine the severity of each AE, SAE and EOSI using the NCI CTCAE v4.03. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.03 as stated in Table 10.3.3.2.1.

Table 10.3.3.2.1: Adverse Event Grading (Severity) Scale

Grade	Description	
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	
2	Moderate: minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]	
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]	
4	Life threatening consequences; urgent intervention indicated	Grade 4 and 5 AEs should always be reported as SAEs
5	Death related to AE	

[a] Instrumental ADL refer to the following examples: preparing meals, shopping for groceries or clothes, using the telephone, managing money.

[b] Self-care ADL refer to the following examples: bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, not bedridden.

10.3.3.3 Causality

The Investigator will determine the relationship of an AE to the study drug and will record it on the source documents and AE eCRF. To ensure consistency of causality assessments, Investigators should apply the guidance in Table 10.3.3.3.1.

Table 10.3.3.3.1: Causality Attribution Guidance

Relationship	Description
Not Related	• Exposure to the IP has not occurred **OR** • The administration of the IP and the occurrence of the AE are not reasonably related in time **OR** • The AE is considered likely to be related to an etiology other than the use of the IP; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP.
Related	• The administration of the IP and the occurrence of the AE are reasonably related in time **AND** • The AE could possibly be explained by factors or causes other than exposure to the IP **OR** • The administration of IP and the occurrence of the AE are reasonably related in time **AND** • The AE is more likely explained by exposure to the IP than by other factors or causes.

Factors suggestive of a causal relationship could include (but are not limited to):

- Plausible temporal relationship
- Absence of alternative explanations
- Rarity of event in a given patient or disease state
- Absence of event prior to study drug exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug action
- Similarity to adverse reactions seen with related drug products
- Abatement of AE with discontinuation of study drug, and/or recurrence of AE with reintroduction of study drug

The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the Investigator's assessment of causality for

individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

10.4 Procedures for Recording Adverse Events

10.4.1 Recording Adverse Events on a eCRF

Investigators should use precise medical terminology when recording AEs or SAEs on the AE eCRF. Avoid colloquialisms and abbreviations.

Record only one diagnosis, sign, or symptom per event field on the AE eCRF (eg, nausea and vomiting should not be recorded in the same entry, but as 2 separate entries).

In order to classify AEs and diseases, preferred terms will be assigned by the Sponsor to the original terms entered on the AE eCRF, using MedDRA (Medical Dictionary for Regulatory Activities) terminology.

10.4.1.1 Diagnosis versus Signs and Symptoms

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Using accepted medical terminology, enter the diagnosis (if known). If not known, enter sign(s) and/or symptom(s). If a diagnosis subsequently becomes available, then this diagnosis should be entered on the AE (or SAE, as appropriate) eCRF, replacing the original entries where appropriate.

10.4.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (eg, cascade events) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the AE eCRF. However, medically important events that may be linked and/or separated in time should be recorded as independent events on the AE eCRF. For example, if severe hemorrhage leads to renal failure, both events should be recorded separately on the AE eCRF.

10.4.1.3 Persistent or Recurrent Adverse Events

A persistent AE (duration of adverse event > 7 days) is one that extends continuously, without resolution, between subject evaluation time points. Events that change in severity necessitate the recording of an additional AE. AEs that do not have a change in severity should be recorded only once on the eCRF.

A recurrent AE is one that occurs and resolves between subject evaluation time points, but then subsequently recurs. All recurrences of the AE should be recorded on the AE eCRF. For example, if a subject has an adverse event of ALT increased that subsequently resolves, but the subject's ALT increases again, that should be reported as two adverse events – the initial ALT increase, and the second ALT increase.

10.4.1.4 Abnormal Laboratory Values

Laboratory test results will be recorded on the laboratory results pages of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for a SAE or EOSI should be reported as such, and recorded in the AE eCRF.

Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF.

A clinical laboratory abnormality is considered clinically significant and should be documented as an AE if not refuted by a repeat test to confirm the abnormality and **any** one or more of the following conditions is met:

- Accompanied by clinical symptoms
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (eg, change of dose, discontinuation of study drug, more frequent follow-up assessments, further diagnostic investigation, etc.)

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after the first dose of study medication that falls outside the laboratory reference range and meets the clinical significance criteria.

This does not apply to any abnormal laboratory result that falls outside the laboratory reference range but that does not meet the clinical significance criteria (these will be analyzed and reported as laboratory abnormalities), those that are considered AEs of the type explicitly exempted by the protocol, or those which are a result of an AE that has already been reported.

For purposes of this study, laboratory tests showing a decreased level of FVIII activity should not be reported as adverse events unless there is an impact to clinical outcomes (eg, increased rate of bleeding, worsening of joint disease).

10.4.1.5 Pre-existing Conditions

A pre-existing condition is one that is present prior to administration of BMN 270. Such conditions should be recorded as medical history on the appropriate eCRF.

A pre-existing condition should be recorded as an AE or SAE during the study **only** if the frequency, intensity, or character of the condition worsens during the study period. It is important to convey the concept that a pre-existing condition has changed by including applicable language in the verbatim description of the event (eg, *more frequent* headaches).

10.4.1.6 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.4.1.5). During the study, any new clinically significant findings and/or abnormalities discovered on physical examination that meet the definition of an AE (or an SAE) must be recorded and documented as an AE or SAE on the AE eCRF.

10.4.1.7 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol (refer to Section 10.2).

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include planned hospitalizations or prolonged hospitalizations to:

- Perform a protocol-mandated efficacy measurement
- Undergo a diagnostic or elective surgical procedure for a pre-existing medical condition that has not worsened
- Insert an in-dwelling IV catheter (such as a Port-a-Cath or other brand, if applicable) for administration of study drug or FVIII replacement therapy
- Receive scheduled therapy (study drug or otherwise) for the study indication

10.4.1.8 Deaths

All deaths that occur during the AE reporting period (refer to Section 10.3.1), regardless of attribution, will be recorded on the AE eCRF and expeditiously reported to the Sponsor as an SAE.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" or "Death of Unknown Cause" on the AE eCRF.

10.4.1.9 Pregnancy

Although not an AE per se, pregnancy in the partner of a subject taking trial medication should be reported expeditiously to the Sponsor to facilitate outcome monitoring by the Sponsor. Pregnancy in partner should be reported during the period up to 5 years after viral infusion.

Pregnancy in a partner should be reported within 24 hours of the site becoming aware of the pregnancy by entering the information on the Pregnancy eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. The Investigator must make every effort to follow the subject's partner (with that partner's consent) through resolution of the pregnancy (delivery or termination) and to report the resolution on the Pregnancy Follow-up eCRF. In the event of pregnancy in the partner of a study subject, the Investigator should make every reasonable attempt to obtain the woman's consent for release of protected health information.

Abortion, whether therapeutic or spontaneous, should always be classified as an SAE (as the Sponsor considers these to be medically significant), recorded on the AE eCRF, and expeditiously reported to the Sponsor as an SAE.

10.5 Reporting Requirements

10.5.1 Expedited Reporting Requirements

All SAEs and EOSI that occur during the course of the AE Reporting Period (refer to Section 10.3.1), whether or not considered related to study drug, must be reported by entering the information in the AE eCRF and submitting to BPV within 24 hours of the site becoming aware of the event. Investigators should not wait to collect information that fully documents the event before notifying BPV of an SAE. BioMarin may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that Investigators submit any information requested by BioMarin as soon as it becomes available. IND safety reports will be submitted within 7 calendar days for fatal or life-threatening unexpected suspected adverse reactions (SUSARs) and within 15 calendar days for other non-life-threatening SUSARs

The Sponsor is responsible for identifying, preparing and reporting all SUSARs to the relevant competent authorities, ethics committees and Investigators in accordance with the requirements identified in the Clinical Trials Regulations.

If the EDC is unavailable, all SAEs should be reported to BPV by completing the SAE Report Form and faxing or emailing the completed form to BPV within 24 hours of the site becoming aware of the event. Once the EDC is available, the information should be entered in the AE eCRF.

10.5.2 Institutional Review Board or Independent Ethics Committee Reporting Requirements

Reporting of SAEs to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) will be done in compliance with the standard operating procedures and policies of the IEC/IRB and with applicable regulatory requirements. Adequate documentation must be obtained by BioMarin showing that the IEC/IRB was properly and promptly notified as required.

10.6 Follow-up of Subjects after Adverse Events

After the initial AE/SAE/EOSI report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs/EOSI will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. Resolution of AEs/SAEs/EOSI (with dates) should be documented on the AE eCRF and submitted to BioMarin Pharmacovigilance and in the subject's medical record to facilitate source data verification.

For some SAEs and EOSI, the Sponsor may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details (eg, hospital discharge summary, consultant report, or autopsy report) deemed necessary to appropriately evaluate the SAE or EOSI report.

10.7 Post-Study Adverse Events

At the last scheduled visit, the Investigator should instruct each subject to report, to the Investigator and/or to BPV directly, any subsequent SAEs that the subject's personal physician(s) believes might be related to prior study drug.

The Investigator should notify the study Sponsor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation, if the Investigator believes that the death or SAE may have been related to prior study drug. The Sponsor should also be notified if the Investigator should become aware of the development of cancer or of a

congenital anomaly in a subsequently conceived offspring of a subject that participated in this study.

10.8 Urgent Safety Measures

The regulations governing clinical trials state that the Sponsor and Investigator are required to take appropriate urgent safety measures to protect subjects against any immediate hazards that may affect the safety of subjects, and that the appropriate regulatory bodies should be notified according to their respective regulations. According to the European Union (EU) Clinical Trial Directive 2001/20/EC, "…in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the patients, the Sponsor and the Investigator shall take appropriate urgent safety measures to protect the patients against any immediate hazard. The Sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the IRB/IEC/REB is notified at the same time."

The reporting period for these events which may require the implementation of urgent safety measures is the period from the time of signing of the ICF through the completion of the last study visit or at the Early Termination Visit (ETV). Investigators are required to report any events which may require the implementation of urgent safety measures to BioMarin within 24 hours.

Examples of situations that may require urgent safety measures include discovery of the following:

- Lack of study scientific value, or detrimental study conduct or management
- Discovery that the quality or safety of the IP does not meet established safety requirements

10.9 BioMarin Pharmacovigilance Contact Information

Contact information for BioMarin Pharmacovigilance is as follows:

BioMarin Pharmaceutical Inc.
Address 105 Digital Drive
Novato, CA 94949
Phone: +1 (415) 506-6179
Fax: +1 (415) 532-3144
E-mail: drugsafety@bmrn.com

The Investigator is encouraged to discuss with the Medical Monitor any AEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is as follows:

Name: [redacted]
Address: [redacted]
Phone: [redacted]
E-mail: [redacted]

11 APPROPRIATENESS OF MEASUREMENTS

The measures of efficacy to be used in this study are standard, ie, widely used and generally recognized as reliable, accurate, and relevant (able to discriminate between effective and ineffective agents). The measures of safety used in this study are routine clinical and laboratory procedures.

The chromogenic substrate FVIII assay and the one-stage clotting FVIII assay are both validated and utilize CE marked reagents. The exploratory FVIII activity assay will be used for exploratory purposes only.

12 STUDY PROCEDURES

12.1 Prestudy

An ICF must be signed and dated by the patient, the Investigator or designee and witness (if required) before any study-related procedures are performed.

12.2 Screening Visit

Screening assessments should be performed within 28 days of BMN 270 infusion (and must be performed within 42 days prior to BMN 270 infusion), while baseline assessments will take place within 7 days prior to BMN 270 infusion (Day 1). Should the screening visit occur within 30 days of the drug infusion, physical examination, vital signs, blood chemistry, LTs, hematology, urine tests, and coagulation tests do not need to be repeated at Baseline.

The following procedures will be performed during the Screening Period:

- Demographics (age, sex, race, ethnicity)
- Full medical history, including hemophilia A history, Hepatitis B, Hepatitis C, and HIV. Subjects with a history of hepatitis B or hepatitis C will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or on-demand FVIII therapy prior to the study should also be collected.
- Complete Physical Examination
- Height and weight
- Vital Signs (systolic and diastolic blood pressure, heart rate, respiration rate, and temperature)
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information) for the previous 12 months
    - Further information on details to be included in documentation of previous bleeding episodes and FVIII usage, refer to the On Site File Binder.
- Distribution of subject diaries and training in diary completion
- Electrocardiogram
- Liver Ultrasound
- Samples for hFVIII Assays
    - Baseline FVIII activity – chromogenic substrate FVIII assay
    - Baseline FVIII activity level – one-stage clotting FVIII assay

  - hFVIII coagulation activity exploratory assay (collected but not tested prior to enrollment)
  - hFVIII inhibitors (Bethesda assay with Nijmegen modification)
  - hFVIII total antibody assay (collected but not tested prior to enrollment)
  - hFVIII protein assay (collected but not tested prior to enrollment)
- Blood sample for AAV5 total antibody (TAb) assay
- Screen for Hepatitis B, Hepatitis C, and HIV if required (subjects with documented negative results 30 days prior to informed consent being obtained do not need to be retested)
  - Hepatitis B screening should include HBsAg, HBsAb, and HBcAb.
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)
- Blood samples for Biomarker testing (including HLA genotyping and FVIII genotyping status)

12.2.1 "Smart Rescreening" Visit

Subjects who undergo smart rescreening must complete the rescreening assessments and receive the infusion within 90 days of signing the original consent. Subjects who do not complete dosing within 90 days will be required to re-consent and undergo all screening procedures. Subjects may not undergo smart rescreening more than once.

If a patient has to be screened again because the original assessments have fallen out of the 28 + 14 day period allowed for Screening (refer to Section 12.2), then only the following assessments need to be performed (rather than the full list indicated in Section 12.2) for the patient to be successfully re-screened for the study:

- Vital signs
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- hFVIII Assays (only the hFVIII inhibitor level (Bethesda assay with Nijmegen modification))
- AAV5 Total Antibody assay
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)

- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)

12.3 Baseline Visit

Baseline values will be recorded from 1 to 7 days prior to the treatment visit. The following procedures will be performed during the Baseline Period:

- Brief physical examination
- Vital signs
- Assessment of Adverse Events and Concomitant Medications
- Documentation of bleeding episodes and FVIII usage (by either subject or clinical information)
- Blood sample for AAV5 TI assay
- Blood sample for AAV5 TAb assay
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
    - ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study).
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)
- Samples for hFVIII Assays
    - Baseline FVIII activity – chromogenic substrate FVIII assay
    - Baseline FVIII activity level – one-stage clotting FVIII assay
    - hFVIII coagulation activity exploratory assay
    - hFVIII inhibitors (Bethesda assay with Nijmegen modification)
    - hFVIII total antibody assay
    - hFVIII protein assay
- PBMC collection for CTL baseline
- Von Willebrand Factor Antigen (VWF:Ag)
- TGA Assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Exploratory biomarker assessments

- Haemo-QoL-A assessment
- EQ-5D-5L
- Hemophilia Activities List (HAL)
- Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific (WPAI+CIQ:HS) questionnaire
- Patient Reported Outcomes, Burdens, and Experiences (PROBE) questionnaire

12.4 Treatment Visit/BMN 270 Infusion Visit (Day 1)

There will be one treatment visit for each subject. Subjects will remain in the clinic for at least 8 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit:

- Brief physical examination
- Assessment of Adverse Events and Concomitant Medications
- AAV5 TAb Assay (sample collected pre-infusion for analysis)
- Fasting lipid panel (blood triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) (sample collected pre-infusion)
    - Subjects will fast for at least 8 hours prior to pre-infusion laboratory sampling on the day of the infusion visit.
- Exploratory biomarker assessments
- BMN 270 Infusion
- Vital Signs
    - Vital signs will be recorded prior to BMN 270 infusion and then every 15 minutes (± 5 minutes) during BMN 270 infusion. Following infusion, vital signs will be monitored every 1 hour (± 5 minutes) for at least 8 hours during the subject's stay in the clinic.
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Collection of samples for PCR testing should occur between 2 and 24 hours after the BMN 270 infusion has been completed

In case of hypersensitivity or adverse drug reaction, safety assessment, including physical examination and vital signs, will be done and additional blood samples will be collected

[redacted]

[redacted]

In-patient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

12.5 BMN 270 Infusion Follow-Up Visits – Weeks 1-26

After BMN 270 has been infused, subjects will return to the study site every week (± 48 hours) during Weeks 1-26. Optional MN services or shortened lab draw-only visits may be conducted for the visits at Week 5, Week 7, Week 9, Week 11, Week 13, Week 15, Week 17, Week 19, Week 21, Week 23, and Week 25.

At the Weeks 1-26 visits, the following procedures will be completed:

12.5.1 Once per week (Weeks 1 through 26)

The following procedures will be performed at one visit per week from Weeks 1 through 26:

- Brief physical examination (complete physical examination at Week 26)
    - For visits where a MN service is being used or a lab draw-only site visit is conducted, physical examination will not be performed.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
    - For visits where a MN service is being used, the service will contact the subject via e-mail or phone call to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use.
- Vital Signs
    - For visits where a MN service is being used or a lab draw-only site visit is conducted, vital signs will not be performed.
- Liver Tests (refer to Table 9.7.8.3.1)
    - LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN & > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN.
- Samples for FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay

- Bethesda assay (with Nijmegen modification) for hFVIII inhibitor level
- FVIII protein assay

12.5.2 Week 1 – Day 4

On Day 4 of Week 1, the following procedures will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Liver Tests (refer to Table 9.7.8.3.1)

12.5.3 Week 1 – Day 8

On Day 8, the following procedures will be performed, in addition to the weekly assessments required in Section 12.5.1:

- PCR of vector DNA in blood, saliva, urine, semen, and stools

12.5.4 Every 2 Weeks (Week 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26)

At Weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, and 26 the following procedure will be performed:

- PBMC collection

12.5.5 Weeks 2, 4, 10, 16, 22, and 26

At Weeks 2, 4, 10, 16, 22, and 26 the following procedure will be performed:

- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)

12.5.6 Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 26

At Weeks 2, 3, 4, 6, 8, 12, 16, 20, 24, and 26, the following procedure will be performed:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Collection to occur until at least 3 consecutive negative results are obtained. Semen samples should continue to be collected and tested through Week 12, even if 3 consecutive negative results in that compartment have been recorded prior to that time point.

12.5.7 Weeks 4, 12, and 26

At Weeks 4, 12, and 26, the following procedure will be performed:

- Haemo-QoL-A assessment
- EQ-5D-5L
- HAL

- WPAI+CIQ:HS
- PROBE

12.5.8 Every 4 Weeks (Weeks 4, 8, 12, 16, 20, and 24) Plus Week 26

At Weeks 4, 8, 12, 16, 20, 24, and 26, the following procedures will be performed:

- Weight (not performed at Week 26)
- FVIII antibody titer

12.5.9 Every 8 Weeks (Weeks 8, 16, and 24)

At Weeks 8, 16, and 24, the following procedures will be performed:

- AAV5 TAb assay
- AAV5 TI assay

12.5.10 Weeks 6, 12, 16, 20, 24, and 26

At Weeks 6, 12, 16, 20, 24, and 26, the following procedures will be performed:

- Exploratory biomarker assessments

12.5.11 Weeks 12 and 26

At Weeks 12 and 26, the following procedures will be performed:

- Urine Tests (refer to Table 9.7.8.2.1)
- VWF:Ag

12.5.12 Week 16

At Week 16, the following procedure will be performed:

- Test for Hepatitis B and Hepatitis C reactivation (only in subjects with evidence of prior exposure to hepatitis B and/or hepatitis C)
    - Subjects who receive therapeutic oral corticosteroids prior to Week 16 do not need to complete the Week 16 reactivation assessment; instead, they will be tested for hepatitis B and hepatitis C reactivation at the time points listed in Table 9.1.6.

12.5.13 Week 20, 24, and 26

At Week 20, 24, and 26, the following procedure will be performed:

- TGA Assay

12.6 Post-Infusion Follow-Up – Weeks 27-52

During Weeks 27-36, subjects will return to the study site weekly (± 48 hours). During Weeks 37-52, subjects will return to the study site every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) (± 1 week). Optional MN services or shortened lab draw-only site visits may be conducted for the visits at Week 27, Week 29, Week 30, Week 31, Week 33, Week 34, Week 35, Week 38, Week 42, Week 46, and Week 50.

At these visits, the following procedures will be completed:

12.6.1 Every Visit

At every visit (Weeks 27-36, 38, 40, 42, 44, 46, 48, 50, and 52), the following procedures will be performed:

- Physical examination
    - Brief physical examination should be performed at all weeks except Week 26, when a complete physical examination should be performed
    - For visits where a MN service is being used or a lab draw-only site visit is conducted, physical examination will not be performed.
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
    - For visits where a MN service is being used, the service will contact the subject via e-mail or phone call to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use.
- Vital Signs
    - For visits where a MN service is being used or a lab draw-only site visit is conducted, vital signs will not be performed.
- Liver Tests (refer to Table 9.7.8.3.1)
    - LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN & > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay

- Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
- FVIII protein assay

12.6.2 Weeks 28, 30, 32, 36, 44, and 52

At Weeks 28, 30, 32, 36, 44, and 52, the following procedure will be performed:

- PBMC collection

12.6.3 Every 4 Weeks (Weeks 28, 32, 36, 40, 44, 48, 52)

At Weeks 28, 32, 36, 40, 44, 48, and 52, the following procedure will be performed:

- Weight

12.6.4 Weeks 32, 36, 44, and 52

At Weeks 32, 36, 44, and 52, the following procedures will be performed:

- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- FVIII antibody titer

12.6.5 Weeks 32, 36, 40, 44, 48, and 52

At Weeks 32, 36, 40, 44, 48, and 52, the following procedures will be performed:

- Exploratory biomarker assessments
- TGA Assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Sample testing to occur until at least 3 consecutive negative sample results have been obtained. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).

12.6.6 Week 32, 36, and 52

At Week 32, 36, and 52, the following procedure will be performed:

- AAV5 TAb Assay
- AAV5 TI Assay

12.6.7 Week 36 and 52

At Weeks 36 and 52, the following procedures will be performed:

- Urine Tests (refer to Table 9.7.8.2.1)

- VWF:Ag

12.6.8 Week 52

At Week 52, the following procedures will be performed:

- Haemo-QoL-A assessment
- EQ-5D-5L
- HAL
- WPAI+CIQ:HS
- PROBE

12.7 Post-Infusion Follow-Up – Years 2-5

During Years 2-5, at applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the patient's home or another suitable location, such as their school or office, to improve access and convenience for patients participating in the study. The Sponsor may select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be allowed for the Q4W (during Year 2) and Q6W (during Years 3-5) visits; the Q12W visits and End of Year during Years 2-5 will not be performed by an MN professional but will be done at the study site.

Subjects who do not respond to BMN 270 treatment [redacted] may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.

Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until

vector shedding has cleared. Such subjects may provide samples on the designated study visit dates either at the sites or through use of a MN professional.

During Years 2-5 of Post-Infusion Follow-up, the following procedures will be completed:

12.7.1 Year 2 – Every 4 Weeks (not required for treatment failure)

During Year 2, every 4 weeks (±2 weeks), the following procedures will be performed:

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1)
    - LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN & > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
    - FVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
    - Sample testing during Year 2 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of semen every 4 weeks during Years 2 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
        - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 4 weeks during Year 2 until vector shedding has cleared. Such subjects may provide samples on the designated study visit dates either at the sites or through use of a MN professional.

12.7.2 Years 3-5 – Every 6 Weeks (not required for treatment failure)

During Years 3-5, every 6 weeks (± 2 weeks), the following procedures will be performed:

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1)
    - LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN & > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
        - If a subject tests positive in the Bethesda assay (with Nijmegen modification) during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.
    - FVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
    - Sample testing during Years 3-5 is not required if at least 3 consecutive samples are clear by the end of Year 2. Subjects who have not had 3 consecutive negative semen samples by the end of Year 2 should continue to have PCR testing of semen every 6 weeks during Years 3-5 until 3 consecutive negative samples are documented (or upon consultation between the Investigator and Medical Monitor).
        - Subjects who meet the definition of treatment failure and wish to follow an abbreviated schedule but who have not cleared vector shedding from all fluids must still provide samples for assessment every 6 weeks during Years 3-5 until vector shedding has cleared. Such subjects may provide samples on the designated study visit dates either at the sites or through use of a MN professional.

12.7.3 Years 2-5 – Every 12 Weeks and End of Year Visits (required for all subjects)

During Years 2-5, subjects will be asked to return to the study site for visits at the following study weeks (±2 weeks):

- Year 2 – Week 64, Week 76, Week 88, Week 104
- Year 3 – Week 116, Week 128, Week 140, Week 156
- Year 4 – Week 168, Week 180, Week 192, Week 208
- Year 5 – Week 220, Week 232, Week 244, Week 260

For each of these years, the last study visit listed (Week 104, Week 156, Week 208, and Week 260) will serve as an End of Year visit. The every 12 week and End of Year visits may not be performed remotely by MN services.

At the every 12 week and End of Year visits, the following procedures will be performed:

- Physical examination
    - Complete physical examination will be performed at the End of Year visits; brief physical examination may be performed at other visits.
- Weight (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.3.1)
    - LTs may be monitored more or less frequently (and in particular when ALT values are ≥1.5x ULN or > ULN & > 2x baseline value) based on discussion between the Medical Monitor and the Investigator and review of subject data, but LTs will be monitored at least twice weekly during periods when a subject's ALT is ≥ 3x ULN.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
    - FVIII protein assay
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1) (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)

- Urine Tests (refer to Table 9.7.8.2.1) (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Vital Signs
- AAV5 TAb Assay
- AAV5 TI Assay
- FVIII antibody titer
- Haemo-QoL-A assessment (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- EQ-5D-5L (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- HAL (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- WPAI+CIQ:HS (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- PROBE (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Exploratory biomarker assessments
- PBMC collection
- VWF:Ag
- TGA Assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
    - Sample testing during Years 2-5 is not required if at least 3 consecutive samples are negative during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive negative semen samples by Week 52 should continue to have PCR testing of 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).

12.8 Early Termination Visit

The Early Termination visit will occur on the date the subject withdraws from the study, even if the date does not correspond to a protocol-specific visit.

If a subject leaves the study prior to the Week 260 visit, the subject will be asked to return to the study site and complete an Early Termination visit. At the Early Termination visit, as many of the following assessments as possible should be done:

- Physical examination

- Weight
- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Vital Signs
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- Urine Tests (refer to Table 9.7.8.2.1)
- Liver Tests (refer to Table 9.7.8.3.1)
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Bethesda assay (with Nijmegen modification) for FVIII inhibitor level
    - FVIII protein assay
- AAV5 TAb Assay
- AAV5 TI Assay
- FVIII antibody titer
- Exploratory biomarker assessments
- PBMC collection
- VWF:Ag
- TGA Assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Sample testing at the ETV is not required if at least 3 consecutive samples were clear during the Post-Infusion Follow-Up period.
- Haemo-QoL-A assessment
- EQ-5D-5L
- HAL
- WPAI+CIQ:HS
- PROBE

12.9 End of Study

The study will end after the last subject yet to complete the last Long-Term Follow-Up visit (Week 260) does so, has transferred to another BMN 270 study, is withdrawn from the study, or discontinues from the study. BioMarin reserves the right to discontinue the study any time for clinical or administrative reasons and to discontinue participation of an individual Investigator or site for clinical or administrative reasons, including, but not limited to, poor enrollment or noncompliance with procedures of the protocol or GCP. In addition, the study may be terminated if, in the opinion of BioMarin, the safety of the study subjects may be compromised.

13 DATA QUALITY ASSURANCE

BioMarin personnel or designees will visit the study site prior to initiation of the study to review with the site personnel information about the IP, protocol and other regulatory document requirements, source document requirements, eCRFs, monitoring requirements, and procedures for reporting AEs, including SAEs.

At visits during and after the study, a CRA will monitor the site for compliance with regulatory documentation, with a focus on accurate and complete recording of data on eCRFs from source documents, adherence to protocol, randomization (if applicable), SAE reporting and drug accountability records.

Data quality control and analysis will be performed by BioMarin or a designee, based on a predefined analysis plan.

14 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

14.1 Statistical and Analytical Plans

The statistical analysis plan (SAP) will provide additional details on the planned statistical analysis. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

An interim analysis is planned after approximately 20 treated HIV-negative subjects have completed the Week 26 visit (or have discontinued study participation prior to Week 26). Data will be reviewed by the DMC, based on the SAP, and a formal recommendation will be made whether to continue the study as designed.

The primary efficacy endpoint for the interim analysis involves hFVIII activity, as measured by chromogenic substrate assay, achieved post-BMN 270 infusion.

[redacted]

The secondary and tertiary endpoints will be summarized descriptively at the interim (Week 26) analysis.

The details of the interim analysis, including the control of Type I error rate, will be specified in the SAP.

14.1.2 Procedures for Accounting for Missing, Unused and Spurious Data

Because the completeness of the data affects the integrity and accuracy of the final study analysis, every effort should be made to ensure complete, accurate, and timely data collection and, therefore, avoid missing data.

Sensitivity analyses will be conducted to assess the impact of missing data on the primary efficacy endpoint analysis. Additional details regarding the handling of missing data will be provided in the SAP.

14.2 Primary Efficacy Endpoint

For the primary efficacy endpoint at Week 52 (ie, the change in the hFVIII activity during Weeks 49-52 post-BMN 270 infusion from baseline, as measured by chromogenic substrate

assay), a one-sample t-test will be used to test the null hypothesis that the change is 0 or less against the alternative hypothesis that the change is greater than 0. Descriptive summaries of the proportions of subjects whose FVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 15, 25 and 30 IU/dL, and the confidence intervals of the proportions will also be provided.

For a subject with a missing value of the primary endpoint, the median value in the subject's last 4-week window containing a valid observation will be used. Additional analyses will be conducted to examine the sensitivity of the results to the handling of missing data, including analysis using observed cases, and a mixed model for repeated measures (MMRM) approach. Further detail will be provided in the SAP.

The analyses for the primary endpoint will be performed using the analysis populations as defined in Section 14.8.

14.3 Secondary Efficacy Endpoints

The primary analyses for the secondary endpoints will be performed on the 35 subjects in the mITT population who will be followed up for approximately 6 months in the non-interventional study 270-902 prior to their enrollment in 270-302. The baseline values will be derived from the prospectively collected data in 270-902.

For the first secondary efficacy endpoint at Week 52 (ie, the change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion from baseline), a one-sample t-test will be performed to test the null hypothesis that the change is 0 or greater against the alternative hypothesis that the change is less than 0.

For the second secondary efficacy endpoint at Week 52 (ie, the change in ABR, annualized bleeding rate, during Weeks 5-52 post-BMN 270 infusion from baseline), a one-sample t-test will be performed to test for non-inferiority of BMN 270 against FVIII prophylaxis (ie, the baseline ABR calculated using subjects' data collected as part of 270-902) using a non-inferiority margin of 3.5, ie, to test the null hypothesis that the change is 3.5 or greater against the alternative hypothesis that the change is less than 3.5. If non-inferiority is demonstrated, the test for superiority of BMN 270 against FVIII prophylaxis will be performed. [redacted]

A sensitivity analysis is planned to analyze ABR using a generalized linear mixed model assuming negative binomial as the underlying distribution. The model will include period (pre- to post-BMN 270 infusion) as the only factor. The actual number of bleeding episodes

will be used as the independent variable with the time period adjustment (animalization) being implemented as the offset.

To assess the impact of missing data, analyses using observed case are planned as sensitivity analyses for the secondary endpoints. Multiple imputation methods may also be performed.

The primary and secondary efficacy hypotheses will be tested hierarchically according to the order described above. Multiple comparison procedures are described in greater detail in the SAP.

14.4 Immunogenicity

Analysis of total and neutralizing antibody response and other immunological parameters will be primarily descriptive and involve both inter-subject and intra-subject comparisons.

14.5 Pharmacodynamic Analyses

Plasma FVIII protein concentrations and FVIII activities determined over the course of the study will primarily be evaluated and summarized with descriptive statistical measures (eg, mean, standard deviation, CV%, min, median, max).

14.6 Safety Analysis

The Medical Dictionary for Regulatory Activities terminology (MedDRA) will be used by the Sponsor to assign system organ class and preferred term classification to events and diseases, based on the original terms entered on the eCRF.

All AEs will be coded using the current version of MedDRA. The incidence of AEs will be summarized by system organ class, preferred term, relationship to study drug, and severity. A by-subject listing will be provided for those subjects who experience a serious AE (SAE), including death, or experience an AE associated with early withdrawal from the study or study drug.

Clinical laboratory data will be summarized by the type of laboratory test. For each clinical laboratory test, descriptive statistics will be provided on Baseline as well as all subsequent visits. Descriptive statistics for physical examination results and vital signs will also be provided.

Detailed statistical methods will be provided in the SAP.

14.7 Determination of Sample Size

Approximately 40 subjects may be dosed in the study. The sample size for this study is 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, a sample size of 40 will provide at least 90% power to demonstrate that the change in hFVIII activity at Weeks 49-52 from baseline 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 secondary endpoints, the analysis will be performed utilizing exogenous FVIII use and bleeding episode data from the 35 subjects whose baseline data will be prospectively collected for approximately 6 months in the non-interventional study 270-902, prior to their enrollment in 270-302. An analytic sample size of 35 will provide at least 90% power to demonstrate that the change in the annualized utilization (IU/kg) of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion from the baseline is less than 0, assuming an effect size of 0.6, using one-sample t-test with a 2-sided significance level of 0.025.

For the analytic sample size calculation of the second secondary endpoint, 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. [redacted] Under this assumption, an analytic sample size of 35 will also have at least 95% power to demonstrate that the change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (ABR) during Week 5 to Week 52 of the study post-BMN 270 infusion from the baseline ABR is less than 3.5 (non-inferiority margin), using a one-sample t-test with a 2-sided significance level of 0.05.

Overall, a sample size of 40 will have greater than 80% power for testing the primary and secondary efficacy endpoints hierarchically at the final analysis with a 2-sided significance level of 0.05.

14.8 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who receive BMN 270 infusion, and the modified intention-to-treat (mITT) population is defined as subjects who receive BMN 270 infusion and are HIV-negative. The mITT population will be used for the

primary efficacy analysis and ITT will be used for the supportive efficacy analysis. The ITT population will also be used for the safety analysis.

14.9 Changes in the Conduct of the Study or Planned Analyses

Only BioMarin may modify the protocol. Any change in study conduct considered necessary by the Investigator will be made only after consultation with BioMarin, who will then issue a formal protocol amendment to implement the change. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC/REB must be sought, and the Investigator should inform BioMarin and the full IRB/IEC/REB within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC/REB must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC/REB prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by BioMarin and the IRB/IEC/REB, and all active subjects must again provide informed consent.

15 DATA MONITORING COMMITTEE

An independent DMC will be convened for this study. The duties of the DMC will include:

- Conducting an ongoing review of individual subject safety and efficacy data during the study.
- Recommending whether to enroll subjects at a different dose level (not to exceed 6E13 vg/kg) based on emerging data from 270-302 and the overall risk/benefit analysis of BMN 270.
- Reviewing ongoing safety and efficacy data for comparability of drug manufacturing lots within 270-302 and between 270-201 and 270-302.
- Making other recommendations on the conduct and reporting of the trial based on their evaluation of clinical data, including data from 270-301.

Details on the composition of the committee, frequency of meetings, and other committee functions and parameters are included in the DMC Charter and in the Statistical Analysis Plan (SAP).

16 COSTS, COMPENSATION, AND SUBJECT INJURY

There will be no charge to study subjects to be in this study. BioMarin will pay all costs of tests, procedures, and treatments that are part of this study. In addition, after IRB/IEC/REB approval, BioMarin may reimburse the reasonable cost of travel for study-related visits in accordance with BioMarin's travel and reimbursement policy. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort related solely to the study subject's disease. Costs associated with such hospitalizations, tests, and treatments should be billed and collected in the way that such costs are usually billed and collected outside the study.

The Investigator should contact BioMarin immediately upon notification that a study subject has been injured by the study drug or by procedures performed as part of the study. Any subject who experiences a study-related injury should be instructed by the Investigator to seek immediate medical treatment at a pre-specified medical institution if possible, or at the closest medical treatment facility if necessary. The subject should be given the name of a person to contact to seek further information about, and assistance with, treatment for study-related injuries. The treating physician should bill the subject's health insurance company or other third party payer for the cost of this medical treatment. If the cost of the medical treatment is not covered by health insurance or another third party that usually pays these costs, then either BioMarin or the institution may pay for reasonable and necessary medical services to treat the injuries caused by the study drug or study procedures. In some jurisdictions, BioMarin is obligated by law to pay for study-related injuries without prior recourse to third party payer billing and/or regardless of fault. If this is the case, BioMarin will comply with the law.

17 CASE REPORT FORMS AND SOURCE DOCUMENTS

Electronic case report forms will be provided for each subject. The Investigator must review and electronically sign the completed eCRF casebook to verify its accuracy.

eCRFs must be completed using a web–based application developed and validated. Study site personnel will be trained on the application and will enter the clinical data from source documentation. Unless explicitly allowed in the eCRF instructions, blank data fields are not acceptable.

In the event of an entry error, or if new information becomes available, the value will be corrected by deselecting the erroneous response and then selecting or entering the factual response. In compliance with ICH GCP Guidelines and 21 CFR Part 11, the system will require the personnel making the correction to enter a reason for changing the value. The documented audit trail will include the reason for the change, the original value, the new value, the time of the correction and the identity of the operator.

BioMarin's policy is that study data on the eCRFs must be verifiable to the source data, which necessitates access to all original recordings, laboratory reports, and subject records. In addition, all source data should be attributable (signed and dated). The Investigator must therefore agree to allow direct access to all source data. Subjects must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent. If direct source document verification of study data by the site monitor is prohibited by institutional policy or local law, then the Investigator must make available facilities and/or personnel to allow GCP-compliant source verification to occur. Examples of such methods include certified copies of records which have study data visible but sensitive information redacted, or other GCP-compliant means agreed between the Investigator and the Sponsor.

A site monitor designated by BioMarin will compare the eCRFs with the original source documents at the study site and evaluate them for completeness and accuracy before designating them as "Source Data Verified" (SDV). If an error is discovered at any time or a clarification is needed, the site monitor, or designee, will create an electronic query on the associated field. Site personnel will then answer the query by either correcting the data or responding to the query. The site monitor will then review the response and determine either to close the query or re–query the site if the response does not fully address the question. This process is repeated until all open queries have been answered and closed.

Before a subject's eCRF casebook can be locked, data fields must be source data verified and all queries closed. Refer to the Study Monitoring Plan for details on which fields must be

source data verified. The Investigator will then electronically sign the casebook, specifying that the information on the eCRFs is accurate and complete. The Data Manager, or designee, will then set the status of the forms, visits, and the entire casebook to Locked. Upon completion of the CSR, an electronic copy of each site's casebooks will be copied to a compact disk (CD) and sent to each site for retention with other study documents.

18 STUDY MONITORING AND AUDITING

Qualified individuals designated by BioMarin will monitor all aspects of the study according to GCP and standard operating procedures for compliance with applicable government regulations. The Investigator agrees to allow these monitors direct access to the clinical supplies, dispensing, and storage areas and to the clinical files, including original medical records, of the study subjects, and, if requested, agrees to assist the monitors. The Investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by BioMarin or its designees.

Members of BioMarin's GCP Compliance Department or designees may conduct an audit of a clinical site at any time before, during, or after completion of the study. The Investigator will be informed if an audit is to take place and advised as to the scope of the audit. Representatives of the FDA or other Regulatory Agencies may also conduct an audit of the study. If informed of such an inspection, the Investigator should notify BioMarin immediately. The Investigator will ensure that the auditors have access to the clinical supplies, study site facilities, original source documentation, and all study files.

19 RETENTION OF RECORDS

The Investigator must retain all study records required by BioMarin and by the applicable regulations in a secure and safe facility. The Investigator must consult a BioMarin representative before disposal of any study records, and must notify BioMarin of any change in the location, disposition or custody of the study files. The Investigator /institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (eg, subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the U.S. or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The Investigator /institution should retain subject identifiers for at least 15 years after the completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 15 years. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by a BioMarin agreement. BioMarin must be notified and will assist with retention should Investigator /institution be unable to continue maintenance of subject files for the full 15 years. It is the responsibility of BioMarin to inform the Investigator /institution as to when these documents no longer need to be retained.

20 USE OF INFORMATION AND PUBLICATION

BioMarin recognizes the importance of communicating medical study data and therefore encourages the publication of these data in reputable, peer-reviewed scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Trial Agreement between BioMarin and the Investigator/Institution. Consideration for authorship of all publications will be based on compliance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals ("Uniform Requirements") of the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/ethical_1author.html) and good publication practices (GPP).

21 REFERENCES

Batts KP & Ludwig J. Chronic hepatitis: an update on terminology and reporting. Am J Surg Pathol 19:1409-1417. 1995.

Bedossa P, Pynard T, French METAVIR Cooperative Study Group. An algorithm for grading activity in chronic hepatitis C. Hepatology 24;289-293. 1996.

Berntorp E, Dolan G, Hay C, Linari S et al. European retrospective study of real-life haemophilia treatment. Haemophilia. 2017;23(1):105-114.

Berntorp E, Peake I, Budde U, Laffan M et. al. von Willebrand's disease: a report from a meeting in the Aland islands. Haemophilia 18 Suppl 6, 1-13. 2012.

Brooks R. EuroQol: the current state of play. Health Policy. 1996;37:53-72.

Chai-Adisaksopha C, Skinner M, Curtis R, et al. Psychometric Properties of the Patient Reported Outcomes, Burdens and Experiences (PROBE) Questionnaire. Blood. 2017;130:5645.

EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208.

George LA, Sullivan S, Teitel J, Cuker A et al. Preliminary results of a phase 1/2 trial of SPK-9001, a hyperactive FIX variant delivered by a novel capsid, demonstrate consistent factor IX activity levels at the lowest dose cohort. Haemophilia 22[Suppl. 4], 151-152. 2016.

Hay CR, DiMichele DM. The principal results of the International Immune Tolerance Study: a randomized dose comparison. Blood 119[6], 1335-1344. 2012.

Haemo-QoL Study Group. Scoring Manual. Available at: http://haemoqol.de/scoring/manual. Last accessed 28 July 2017.

Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia. Blood 122[22], 3568-3574. 2013.

Manno CS, Pierce GF, Arruda VR, Glader B et. al. Successful transduction of liver in hemophilia by AAV-Factor IX and limitations imposed by the host immune response. Nat Med 12[3], 342-347. 2006.

Miesbach W, Tangelder M, Klamroth R, Schutgens R et al. Updated results from a dose escalating study in adult patients with haemophilia B with AMT-060 (AAV5-hFIX) gene therapy. Haemophilia 22[Suppl. 4], 151-152. 2016.

Mingozzi F and High KA. Immune responses to AAV vectors: overcoming barriers to successful gene therapy. Blood 122[1], 23-36. 2013.

Nathwani AC, Reiss UM, Tuddenham EG, Rosales C et. al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. N Engl J Med 371[21], 1994-2004. 2014.

Nathwani AC, Rosales, C, McIntosh J, Rastegarlari G et. al. Long-term safety and efficacy following systemic administration of a self-complementary AAV vector encoding human FIX pseudotyped with serotype 5 and 8 capsid proteins. Mol Ther 19[5], 876-885. 2011.

Nathwani AC, Tuddenham EG. Epidemiology of coagulation disorders. Baillieres Clin Haematol 5[2], 383-439. 1992.

Pasi KJ, Rangarajan S, Kim B et al. Achievement of Normal Circulating Factor VIII Activity Following BMN 270 AAV5-FVIII Gene Transfer: Interim, Long-Term Efficacy and Safety Results from a Phase 1/2 Study in Patients with Severe Hemophilia A. Blood 130[Suppl. 1], 603. 2017.

Rangarajan S, Kim B, Lester W et al. Achievement of normal factor VIII activity following gene transfer with valoctocogene roxaparvovec (BMN 270): Long- term efficacy and safety results in patients with severe hemophilia A. Haemophilia 24[Suppl. 5], 65. 2018

Reilly M. WPAI Scoring. 2002. Available at: http://www.reillyassociates.net/ WPAI_Scoring.html. Last accessed 28 July 2017.

Recht M, Neufeld EJ, Sharma VR, Solem CT et al. Impact of Acute Bleeding on Daily Activities of Patients with Congenital Hemophilia with Inhibitors and Their Caregivers and Families: Observations from the Dosing Observational Study in Hemophilia (DOSE). Value in Health. 2014;17:744-748.

Rentz A, Flood E, Altisent C, Bullinger M et al. Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia. Haemophilia 2008;14(5):1023-34.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391-397.

Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS et. al. Guidelines for the management of hemophilia 128. Haemophilia 19[1], e1-47. 2013.

Stonebraker JS, Brooker M, Amand RE, Farrugia A et. al. A study of reported factor VIII use around the world. Haemophilia 16[1], 33-46. 2010.

United States Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2014. Available at https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/458/plasma-hiv-1-rna--viral-load--and-cd4-count-monitoring. Last accessed 28 July 2017.

Van Genderen FR, Westers P, Heijnen L, De Kleijn P et al. Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List. Haemophilia. 2006;12:36-46.

Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of hypotheses. J Biopharm Stat. 2005; 15:929–942.

22 INVESTIGATOR RESPONSIBILITIES

22.1 Conduct of Study and Protection of Human Patients

In accordance with FDA Form 1572 and/or principles of ICH E6 GCP, the Investigator will ensure that:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes, and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and/or ICH E6 Sections 2.9 and 4.8 are met. As well, he or she will ensure that IRB/IEC review and approval in 21 CFR Part 56 and/or ICH E6 Section 2.6 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64 and/or ICH E6 Section 4.11.
- He or she has read and understands the information in the Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- Adequate and accurate records in accordance with 21 CFR 312.62 and/or ICH E6 Section 4.9 are kept, and those records are available for inspection in accordance with 21 CFR 312.68 and/or ICH E6 Section 4.9.7.
- The IRB/EC/REB complies with the requirements of 21 CFR Part 56, ICH E6 Section 3.0, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/EC/REB. Additionally, he or she will not make any changes in the research without IRB/EC/REB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312 and/or ICH E6.

23 SIGNATURE PAGE

Protocol 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 at a dose of 4E13 vg/kg in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions

Protocol Number: 270-302 Amendment 4

I have read the forgoing protocol and agree to conduct this study as outlined. I agree to conduct the study in compliance with all applicable regulations and guidelines, including ICH E6 , as stated in the protocol, and other information supplied to me.

Investigator Signature Date

Printed name: _____

Accepted for the Sponsor:

Medical Monitor Signature Date

Printed name: [redacted]

24 APPENDICES

Appendix 1: Sampson's Anaphylaxis Criteria

According to the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) Second Symposium on the definition and management of anaphylaxis, anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

e. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease is systolic BP

f. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Source: Sampson, 2006.

25 PROTOCOL AMENDMENT TEXT REVISIONS

The following table summarizes the revisions made to the protocol and relates the changes to the appropriate rationale (see pages 2-3). Added text is indicated by underlined font and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	Revision	Rationale
Synopsis/Study Design and Plan	Subjects who do not respond to BMN 270 treatment [redacted] may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.	4
9.1/Overall Study Design and Plan	Subjects who do not respond to BMN 270 treatment [redacted] may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.	4
Table 9.1.1 through Table 9.1.5	The Direct Thrombin Activity assay assessment has been removed.	3
Table 9.1.1 notes	[e] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.3.1 for liver tests. ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study). [g] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, ~~ABO blood typing,~~ and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay, ~~Direct Thrombin Activity test,~~ and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.	3, 4
Table 9.1.2 notes	[e] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to	1, 3

Section No./Title	Revision	Rationale
	discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay~~, Direct Thrombin Activity test,~~ and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor. [g] The scheduled visits at Week 5, Week 7, Week 9, Week 11, Week 13, and Week 15 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.	
Table 9.1.3 notes	[e] Blood samples will be collected from subjects to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay~~, Direct Thrombin Activity test, and~~ any other exploratory assessments) will be performed only as deemed necessary by the Sponsor. [f] The scheduled visits at Week 17, Week 19, Week 21, Week 23, Week 25, Week 27, Week 29, Week 30, and Week 31 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.	1, 3
Table 9.1.4 notes	[d] Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated	1, 3

Section No./Title	Revision	Rationale
	above, testing of these samples (including those for TGA assay~~, Direct Thrombin Activity test,~~ and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor. [e] The scheduled visits at Week 33, Week 34, Week 35, Week 38, Week 42, Week 46, and Week 50 may be performed by a mobile nursing (MN) professional at the subject's home or another suitable location (if the subject has given written informed consent to participate in MN visits), or at the site as a shortened lab draw-only visit. The MN service or site will collect blood samples at these visits. For site lab draw-only visits, sites will contact the subject via phone call or e-mail to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. For MN visits, the service will collect this information. The physical examination and vital signs assessments listed in the Schedule of Events will not be performed at these MN or lab draw-only visits.	
Table 9.1.5 notes	[e] Blood samples will be collected to evaluate biochemical, molecular, cellular, and genetic/genomic aspects relevant to hemophilia A disease, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A. While exploratory samples will be collected at the time points indicated above, testing of these samples (including those for TGA assay~~, Direct Thrombin Activity test,~~ and any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.	3
9.7.2.1/FVIII Activity	Subjects who do not respond to BMN 270 treatment (ie treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 or inability to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes, in the judgment of the Investigator) may, at the Investigator's discretion and after discussion with the Medical Monitor or Sponsor-designated Data Monitor, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.	4
9.7.7/Exploratory Assessments	Blood samples will be collected from subjects at the time points indicated in Table 9.1.1, Table 9.1.2, Table 9.1.3, Table 9.1.4, and Table 9.1.5 to evaluate biochemical, molecular, cellular, ~~ABO blood typing,~~ and genetic/genomic aspects relevant to hemophilia A, coagulation, and/or AAV gene transfer, and to develop assays used for these evaluations. Subjects may choose to opt out of the exploratory genetic/genomic research being done to study or try to discover genes that are not yet known to be associated with hemophilia A.	4
9.7.8.2/Clinical Laboratory Assessments	MN visits may also be available during Year 1 at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 30, 31, 33, 35, 38, 42, 46, and 50 (as indicated in the Schedule of Events).	1

Section No./Title	Revision	Rationale
Table 9.7.8.2.1	ABO blood typing has been added to this table, with the note: *ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study).	4
9.7.8.3/Vital Signs, Physical Examinations, and Other Safety Observations	A complete physical examination is necessary during Screening/Baseline, at Week 26 and 52 and every 52 weeks thereafter; at other visits, brief physical examinations may be performed at the discretion of the Investigator based on the subject's clinical condition. Particular attention should be given to signs of bleeding, as well as assessing possible hemarthroses. During Year 1, at visits where the MN services are used or shortened lab draw-only visits are conducted at the sites, the physical examination and vital signs assessments indicated in the Schedule of Events will not be performed.	1
10.2.1/Events of Special Interest	The following EOSI need to be reported to the Sponsor within 24 hours of site awareness, irrespective of seriousness, severity or causality: • Development of anti-FVIII inhibitory antibodies (inhibitors)	2
12.3/Baseline Visit	Baseline values will be recorded from 1 to 7 days prior to the treatment visit. The following procedures will be performed during the Baseline Period: • Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1) ○ ABO blood typing assessment should be performed as part of the hematology assessment (at Baseline, or at another regularly scheduled visit prior to the end of the subject's participation in the study). • ~~Direct Thrombin test~~	3, 4
12.4/Day 1 Visit	There will be one treatment visit for each subject. Subjects will remain in the clinic for at least 8 hours for the BMN 270 Infusion Visit. The following procedures will be performed during the BMN 270 Infusion Visit: • Exploratory biomarker assessments	4
12.5/Weeks 1-26	After BMN 270 has been infused, subjects will return to the study site every week (± 48 hours) during Weeks 1-26. Optional MN services or shortened lab draw-only site visits may be conducted for the visits at Week 5, Week 7, Week 9, Week 11, Week 13, Week 15, Week 17, Week 19, Week 21, Week 23, and Week 25. At the Weeks 1-26 visits, ~~, when~~ the following procedures will be completed:	1

Section No./Title	Revision	Rationale
12.5.1/Once per Week (Weeks 1-26)	The following procedures will be performed at one visit per week from Weeks 1 through 26: • Brief physical examination (complete physical examination at Week 26) o For visits where a MN service is being used or a lab draw-only site visit is conducted, physical examination will not be performed. • Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) o For visits where a MN service is being used, the service will contact the subject via e-mail or phone call to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use. • Vital Signs o For visits where a MN service is being used or a lab draw-only site visit is conducted, vital signs will not be performed.	1
12.5.10/Weeks 6, ~~13~~ 12, 16, 20, 24, and 26	At Weeks 6, ~~13~~12, 16, 20, 24, and 26, the following procedures will be performed: • Exploratory biomarker assessments	1
12.5.11/Weeks 12 and 26	At Weeks 12 and 26, the following procedures will be performed: • Urine Tests (refer to Table 9.7.8.2.1) • VWF:Ag	1
~~12.5.12/Week 13 and 26~~	~~At Weeks 13 and 26, the following procedures will be performed:~~ • ~~Direct Thrombin test~~ • ~~VWF:Ag~~	1, 3
12.6/Weeks 27-52	During Weeks 27-36, subjects will return to the study site weekly (± 48 hours). During Weeks 37-52, subjects will return to the study site every 2 weeks (Week 38, 40, 42, 44, 46, 48, 50, and 52) (± 1 week). Optional MN services or shortened lab draw-only site visits may be conducted at Week 27, Week 29, Week 30, Week 31, Week 33, Week 34, Week 35, Week 38, Week 42, Week 46, and Week 50.	1

Section No./Title	Revision	Rationale
12.6.1/Every Visit	At every visit (Weeks 27-36, 38, 40, 42, 44, 46, 48, 50, and 52), the following procedures will be performed: • Physical examination o Brief physical examination should be performed at all weeks except Week 26, when a complete physical examination should be performed o <u>For visits where a MN service is being used or a lab draw-only site visit is conducted, physical examination will not be performed.</u> • Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use) o <u>For visits where a MN service is being used, the service will contact the subject via e-mail or phone call to collect information regarding adverse events, changes to concomitant medications, bleeding episodes, and FVIII use.</u> • Vital Signs o <u>For visits where a MN service is being used or a lab draw-only site visit is conducted, vital signs will not be performed.</u>	1
12.6.2/Weeks 28, 30, 32, ~~34,~~ 36, 44, and 52	At Weeks 28, 30, 32, ~~34,~~36, 44, and 52, the following procedure will be performed: • PBMC collection	1
12.6.7/Week ~~38~~ <u>36</u> and 52	At Weeks ~~38~~ <u>36</u> and 52, the following procedures will be performed: • Urine Tests (refer to Table 9.7.8.2.1) • ~~Direct Thrombin test~~ • VWF:Ag	1, 3
12.7/Years 2-5	Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 or inability to maintain independence from prophylactic FVIII replacement therapy due to joint bleeding episodes, in the judgment of the Investigator) may, at the Investigator's discretion and after discussion with the Medical Monitor <u>or Sponsor-designated Data Monitor</u>, follow an abbreviated visit schedule after Week 52 of the study by attending only the Q12W and End of Year visits during Years 2-5.	4

Section No./Title	Revision	Rationale
12.7.3/Years 2-5 Every 12 Weeks and End of Year Visits	At the every 12 week and End of Year visits, the following procedures will be performed: • ~~Direct Thrombin test~~	3
12.8/ETV	At the Early Termination visit, as many of the following assessments as possible should be done: • ~~Direct Thrombin test~~	3