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

NCT Number: NCT04323098

Applicant/MAH: BioMarin Pharmaceutical Inc.

Version Date: 25 May 2021

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients
Protocol Number:	270-303
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	IND #: 017659 2018-004616-21
Indication:	Hemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3b
Sponsor's Responsible Medical Monitor:	PI MD, MHS PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	6E13 vg/kg
Study Population:	Males aged 18 or older
Date of Original Protocol:	28 February 2020

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

PROTOCOL NUMBER:

270-303

STUDY SITES:

Approximately 10 sites worldwide.

PHASE OF DEVELOPMENT:

Phase 3b

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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 includes 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 and/or subcutaneous injection of a bi-specific monoclonal antibody, emicizumab, as prophylaxis 1-4 times per month. 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 annualized bleeding rate [ABR] of 1-4 with prophylaxis treatment in a recently published retrospective observational study 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 and between 20-60 in 6 prospective

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:

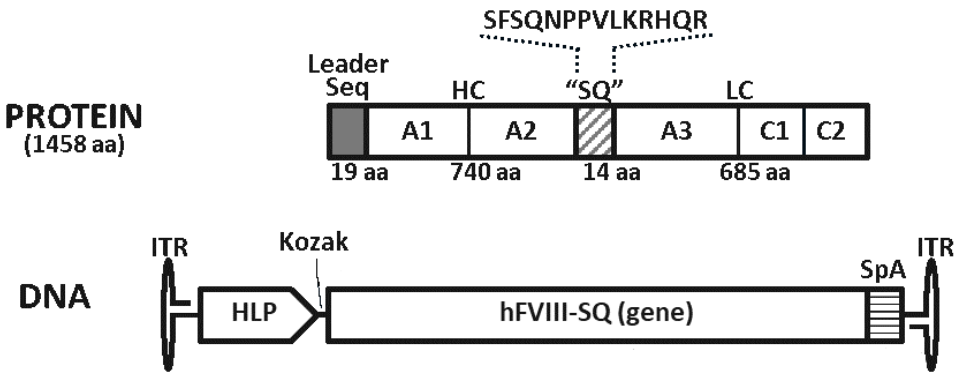
FVIII interventional studies). The consequence of multiple bleeding events is the development of debilitating multiple-joint arthropathy and substantially increased risk of death. Chemical modification (eg, direct conjugation of polyethylene glycol (PEG) polymers) and bioengineering of FVIII (eg, FVIII-Fc 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. While emicizumab prophylaxis has yielded lower bleed rates compared to prior FVIII prophylaxis, it does not physiologically recapitulate the coagulation system, requires chronic, life-long therapy, and still necessitates the use of on-demand FVIII concentrates for treatment of breakthrough bleeds. 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. HA 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 6.7 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.

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).

Figure 1: hFVIII-SQ Vector Genome and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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 vector genomes [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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive).

Three-year results from 270-201 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile. Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm pan-lobular and otherwise healthy liver transduction at 2.5 years. In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201.

Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were started on corticosteroids by Week 3 (either therapeutically, in response to an ALT elevation, or prophylactically), whereas in 270-301 subjects received corticosteroids only in response to an alanine aminotransferase (ALT) elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion, showed later advent of first ALT elevations, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation when compared with subjects in 270-301 (20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity. Recently published data from 270-201 suggests that

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:

corticosteroids may have assisted in rescue or protection of FVIII levels during elevations of ALT and in resolution of elevated ALT levels in some subjects.

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

OBJECTIVES:

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

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:

The safety objectives of the study are to:

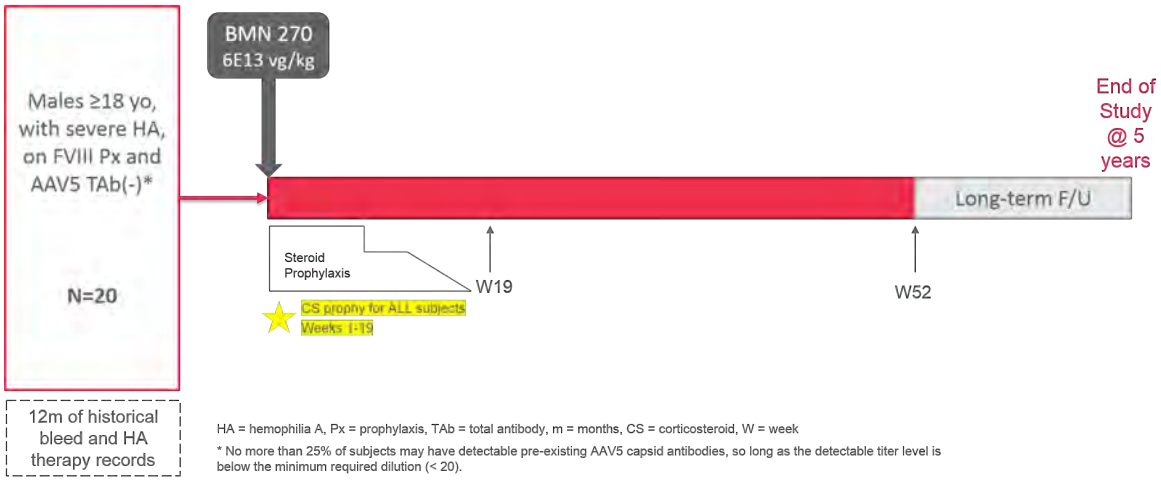
- Evaluate the safety of BMN 270 with prophylactic corticosteroids during the first 52 weeks following intravenous infusion of BMN 270
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

STUDY DESIGN AND PLAN:

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 10 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of BMN 270 infusion (Figure 2). Therapeutic corticosteroids, as needed for ALT elevations and/or FVIII decline, will also be available post-infusion.

Figure 2: 270-303 Study Schema



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:

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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. 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. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and consultation with the Investigator and the Medical Monitor. Therapeutic oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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:**

Additionally, 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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

NUMBER OF SUBJECTS PLANNED:

Approximately 20 subjects will be enrolled into the study, with at least 16 AAV5 TAb-negative and up to 25% AAV5 total antibodies (TAb) detectable but below the minimum required dilution.

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 hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
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.

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:

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 viral vector DNA below the limit of detection.
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. Up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the detectable titer level is below the minimum required dilution (< 20).
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 upper limit of normal (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.

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:

4. Most recent, prior FibroScan or liver biopsy showing significant fibrosis of 3 or 4 as rated on a scale of 0-4 on the Batts-Ludwig or METAVIR 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 $\geq$ 1.5 mg/dL.
8. Liver cirrhosis of any etiology as assessed by liver ultrasound/FibroScan.
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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.
16. 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 corticosteroid treatment outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.

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:**

19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

Optional Liver Biopsy Inclusion and Exclusion Criteria

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

8. Able to sign informed consent and comply with requirements for the optional liver biopsy
9. Documentation of FVIII activity level ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist or radiologist, would make liver biopsy contraindicated. This includes (but is not limited to): abnormalities detected on liver ultrasound performed within 28 days of procedure or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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

Each subject will receive a single intravenous infusion of BMN 270 at 6E13 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.

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:

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 from baseline in the annualized utilization (IU/kg/year) and infusion rate (number/year) of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis.
- Change from baseline in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) during Week 5 to Week 52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion

Tertiary efficacy endpoints:

- Change from baseline in the EQ-5D-5L score at Week 52 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 post-BMN 270 infusion.
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 post-BMN 270 infusion.

<u>Safety:</u>

The following safety outcome measurements will be assessed:

- Incidence of adverse events (AEs) and serious AEs (SAEs)

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 in clinical laboratory tests (serum chemistry and hematology)
- Change in vital signs
- Change in physical examination
- Vector shedding (blood, urine, semen, stool, saliva)
- Liver tests (LTs, including ALT, AST, GGT, lactate dehydrogenase [LDH], total bilirubin, and alkaline phosphatase)
    - 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.
- Immune response to FVIII transgene product and AAV5 capsid proteins
- Immunological assessments, including hFVIII TAb, interferon gamma (IFNg) ELISpot, complement, and an exploratory biomarker panel.

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 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects who have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening.

For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

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:**

Analysis Population

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

Subjects with an AAV5 antibody titer detectable but below the minimum required dilution will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post-BMN 270 infusion.

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. Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels ≤ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose FVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 IU/dL, and the confidence intervals of the proportions will also be provided.

The analyses of the secondary and tertiary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion:

- Change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in

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:

the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis

- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment during Weeks 5-52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Weeks 27-52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis from baseline

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

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.

The final analysis for the study will be performed after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52).

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

Details of the planned analyses will be specified in the SAP.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAV	adeno-associated virus
ABR	annualized bleeding rate
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CBA	cytokine bead array
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CL	clearance
cNBA	FVIII chromogenic Nijmegen Bethesda Assay
CRA	clinical research associate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
ED	exposure days
EDC	electronic data capture
EMA	European Medicines Agency
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	hemophilia A
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
HLP	hybrid human liver-specific promoter
IB	investigator's 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
IFNg	interferon gamma
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MN	mobile nursing
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
PRO	patient-reported outcome
PROBE	Patient Reported Outcomes, Burdens, and Experiences
rhFVIII	recombinant human FVIII
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SOI	Statement of Investigator
SOP	standard operating procedure
SQ	SFSQNPPVLKRHQR

SUSAR	serious unexpected suspected adverse reactions
TAb	total antibody
TGA	thrombin generation assay
TI	transduction inhibitor
ULN	upper limit of normal
vg	vector genomes
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) 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 will be provided to BioMarin or its designee. The Investigator will provide the IRB/IEC 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 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 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 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 ICF, in compliance with ICH E6 (Section 4.8), 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. BioMarin and the IRB/IEC 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 (Iorio, 2019). 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 hybrid human liver-specific transcription promoter (HLP). 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 intravenous (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 European Medicines Agency (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

Ongoing clinical studies for BMN 270 include:

- 270-201, a phase 1/2, dose-escalation study in patients with severe HA
- 270-203, a phase 2 study in patients with severe HA who have anti-AAV5 antibody titers
- 270-301, a phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 vector genomes [vg]/kg dose level
- 270-302, a phase 3 study in patients with severe HA who receive BMN 270 at the 4E13 vg/kg dose level

A comprehensive review of safety, efficacy, and immunogenicity results from these studies 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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 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.

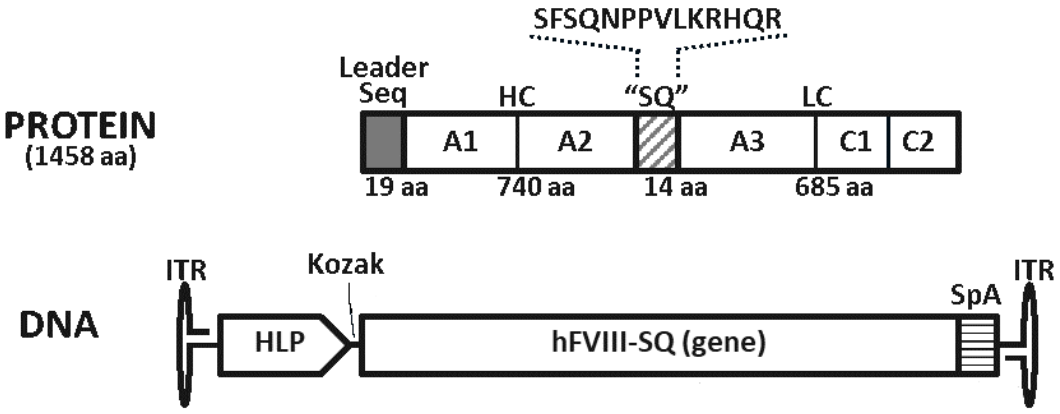
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. Hemophilia A is well-suited for a gene replacement approach 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 6.7years; Nathwani, 2018) 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 and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with

severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive). With the exception of 270-203, subjects in other BMN 270 studies who are AAV5-antibody positive have been excluded. In 270-303, up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the detectable titer level is below the minimum required dilution (< 20). It is expected that subjects with such a low detectable titer level will respond in a similar manner to subjects who are AAV5 capsid antibody negative.

Three-year results from 270-201 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile (Pasi, 2020). Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm pan-lobular and otherwise healthy liver transduction at 2.5 years. In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201 (Pasi, 2020).

Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were started on corticosteroids by Week 3 (either therapeutically, in response to an alanine aminotransferase [ALT] elevation, or prophylactically), whereas in 270-301 subjects received corticosteroids only in response to an ALT elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion, showed later advent of first ALT elevations, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation when compared with subjects in 270-301 (20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity. Recently published data from 270-201 suggests that corticosteroids may have assisted in rescue or protection of FVIII levels during elevations of ALT and in resolution of elevated ALT levels in some subjects (Pasi, 2020).

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

7.3.1 Optional Liver Biopsy Rationale

The usual pattern of response in hFVIII activity observed so far after administration of BMN 270 demonstrates peak expression levels during the first 6-12 months post-treatment followed by a decline to a steady-state level of expression thereafter. One of the explanations may lie in the kinetics of vector genome processing, which involves a series of steps such as DNA degradation and repair, annealing, and circularization that can result in the formation of stable, double-stranded, circularized transgene DNA forms. It is these circularized DNA species that are thought to be associated with long-term, persistent expression of the gene product in target cells. Examination of transduced hepatocytes from subjects treated with BMN 270 in the 270-303 study will help to establish whether DNA circularization may occur and could account for the long-term hFVIII expression observed in humans.

Additionally, health of the liver after gene transduction has been monitored indirectly by periodic assessments of hepatic enzymes released into the blood stream. Transient, post-treatment elevations in ALT levels have been observed in the majority of subjects, as well as inter-subject variability in post-therapy FVIII activity levels. Neither the reasons for nor the significance of the ALT elevations or the variations in response to FVIII gene therapy are known. Moreover, the effects of BMN 270 on hepatic tissue structure and function are also currently unknown. Finally, a call to incorporate liver biopsy sub-studies into gene therapy trials for hemophilia has been issued by medical and scientific leaders in the field to help illuminate these and other questions (National Hemophilia Foundation, 2019).

The purpose of this exploratory sub-study is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in FVIII activity levels observed after gene therapy with BMN 270. With use of prophylactic corticosteroids, it is believed that there will be stable hepatic function and FVIII activity expression, with tolerance of prophylactic corticosteroid therapy and no change to the risk of thromboembolism. This sub-study aims to evaluate the effect on the liver by performing liver biopsies at approximately Week 26, Week 52, and/or during Years 2-5.

7.4 Summary of Overall Risks and Benefits

BMN 270 has an acceptable safety and tolerability profile that supports a positive benefit-risk assessment. Single infusions have been generally well tolerated by treated subjects across all investigated doses. All subjects have successfully completed their full-dose infusion of BMN 270, with no infusions requiring permanent termination prior to completion due to AEs. No deaths have been reported in any of the BMN 270 studies, and no

participants discontinued from studies as a result of an AE. Frequency of adverse events decreased over time with no delayed adverse drug reactions.

Infusion reactions associated with BMN 270 administration included symptoms such as maculopapular rash, urticaria, nausea, diarrhea, watery eyes, rigors, chills, myalgia, fever, tachycardia and hypotension emerging within 24 hours of receiving BMN 270. All of these events subsided without clinical sequela within 48 hours following medical management Infusion-related reactions were effectively mitigated by managing infusion rate and medications.

Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) was observed in most subjects administered BMN 270 shortly after dosing, with no symptoms or sequelae suggestive of clinically significant hepatocyte injury or liver dysfunction. In almost all subjects, ALT elevations decreased quickly following corticosteroid treatment. There were differences in the use of corticosteroids across studies. Subjects in 270-201 received corticosteroids an average of 8 weeks earlier following BMN 270 infusion than the mITT population in 270-301, were more likely to avoid a significant decline in FVIII activity concurrently with an ALT elevation, and saw a more robust recovery of FVIII activity upon the first use of corticosteroids, than did the subjects in the mITT population in 270-301. Despite the clinical response to steroids, no associations between safety parameters (transient ALT rises), or efficacy as measured by FVIII activity levels were found to be temporally associated with anti-AAV5 antibody or cellular immune responses.

In this study, corticosteroids will be initiated prophylactically (ie, prior to any increase in ALT) on Day 1, prior to the BMN 270 infusion. Close monitoring of ALT and FVIII activity is recommended to enable early and timely initiation of therapeutic corticosteroid treatment (ie, in response to an increase in ALT). During prophylactic and therapeutic corticosteroid treatment, emphasis will be placed on a slow taper of the dose, with the aim of achieving ALT levels near the subject's baseline to limit hepatocellular toxicity and possibly ameliorate reduction of transgene expression over the period when ALT elevations have been observed.

At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII activity above 50 IU/dL at 52 weeks post-infusion. Subjects in that cohort 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.

In 270-301, an interim analysis has shown increased FVIII activity in the majority of subjects to mild HA or normal levels at 26 weeks post-infusion, also with markedly decreased bleeding compared with pre-study rates and the ability to discontinue prophylactic FVIII

infusions. All subjects who will be included in the final analysis have been dosed with 6E13 vg/kg and continue to be followed.

The current data available has shown an established positive benefit:risk profile for BMN 270 at the 6E13 vg/kg dosing level, although the impact of prophylactic corticosteroids requires further investigation. 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 270-303 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LTs 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 the risks and benefits of treatment with BMN 270, refer to the current version of the Investigator's Brochure.

7.4.1 Optional Liver Biopsy Risks and Benefits

Liver biopsy is considered a safe procedure, with serious complications occurring less than once in every 10,000 procedures (Grant, 2004). Although the theoretical risks of significant complications are extremely small, the main complications would include bleeding and bile leakage. Another theoretical complication is infection at the needle insertion site; the sterile technique used makes this risk extremely small.

The most common problems include mild pain and a minor decrease in blood pressure. More serious complications, such as bleeding, infection, and injury to nearby organs, are very rare, but the subject will be monitored appropriately to ensure correct management should any of these occur. Any complications related to the liver biopsy should be reported as adverse events, as outlined in Section 10. The liver biopsy is a standard investigation, and will be explained more fully by the experienced clinician performing the biopsy.

Each subject who participates in this optional sub-study will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. Timing of the liver biopsies will occur at Weeks 26, 52, and/or during Years 2-5. Safety will be assessed by adverse event reporting and clinical laboratory assessments. Per the Investigator's discretion and/or according to local guidelines, the subject may be kept in overnight following the liver biopsy for additional safety monitoring; such an overnight stay would not be considered a hospitalization for serious adverse event (SAE) reporting purposes (refer to Section 10.4.1.7).

There is no direct benefit from participating in this study other than contributing to understanding the mechanism of action of BMN 270. Consenting into this specific sub-study is optional and will not have any effect on the subject's continued participation in 270-303.

8 STUDY OBJECTIVES

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

The safety objectives of the study are to:

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

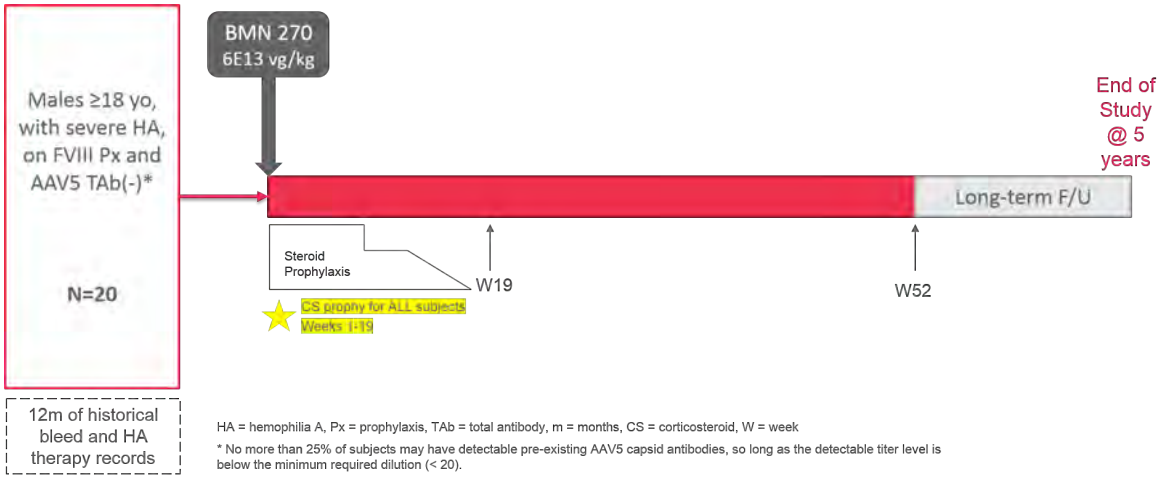
9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 10 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. Post-infusion, subjects will be eligible to receive on-demand corticosteroids, as indicated. (Figure 9.1.1).

Figure 9.1.1: 270-303 Study Schema



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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity $\geq$ 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. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and consultation with the Investigator and the Medical Monitor. Therapeutic oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

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 the optional liver biopsy (Table 9.1.5) 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)[l]
	Screening		Smart Rescreening[i] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[k]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Informed consent	X	X[o]			
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 hemophilia therapy usage for previous 12 months (by either subject or clinical information)		X	X	X	
Distribution of subject diaries and training in their use[b]		X			
Electrocardiogram		X			
Liver Ultrasound/FibroScan		X			
hFVIII Assays[c]		X	X[j]	X	
hFVIII TAb		X		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
Fasting FibroTest					X
Urine Tests[e]		X	X	X	
Liver Tests[e]		X	X	X	
AAV5 TAb Assay (CDx)[f]	X	X	X		X
Immunogenicity AAV5 TAb Assay				X	X
AAV5 TI Assay				X	X
IFNg ELISpot				X	
Plasma, PBMC, and RBC collection for exploratory biomarkers[h]				X	
Complement Panel				X	

Assessment	Prior to BMN 270 Infusion				BMN 270 Infusion Visit (Day 1)[l]
	Screening		Smart Rescreening[i] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[k]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Biomarker testing[g]		X			
Serum for exploratory biomarkers[h]		X			X
Exploratory CK18 and Grp78 assessment		X		X	
TGA Assay[h]				X	
Haemo-QoL-A assessment				X	
EQ-5D-5L				X	
WPAI+CIQ:HS				X	
PROBE				X	
PCR of vector DNA in blood, saliva, urine, semen, and stools				X	X
Pharmacokinetics				X[n]	
BMN 270 Infusion					X
Hypersensitivity blood assessments[m]					X

* 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] 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.

[c] Includes baseline FVIII activity (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), coagulation exploratory assay, chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, 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).

[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 at Screening.

[f] Screening, Smart Re-screening, and Infusion Day samples will be tested using the CDx AAV5 total antibody (TAb) assay. During Screening, the CDx AAV5 TAb assay test may be done first, under a standalone informed consent form, before the main ICF for the study is signed and further screening procedures are performed. If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening. Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.

[g] Includes HLA genotyping and FVIII genotyping.

[h] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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, as well as testing of the thrombin generation assay (TGA) sample, will be performed only as deemed necessary by the Sponsor.

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

[l] With the exception of the collection of samples for polymerase chain reaction (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 analysis (blood, saliva, urine, semen, stool) should be collected between 2 and 24 hours after the infusion has been completed.

[m] In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory cytokine bead array (CBA) to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

[n] Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

[o] If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

Table 9.1.2: Schedule of Events-Post-Infusion Follow-Up (Week 1-20)

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	2[f]	3[f]	4	5[f]	6[f]	7[f]	8	9[f]	10[f]	11[f]	12	13[f]	14[f]	15[f]	16	17[f]	18	19[f]	20
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
Physical examination[a]				X				X				X				X		X		X
Weight[a]				X				X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs				X				X				X				X				X
Blood chemistry, hematology, and coagulation tests[b]				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	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	X			X				X				X				X				X
Immunogenicity AAV5 TAb Assay				X				X								X				
AAV5 TI Assay				X				X								X				
hFVIII TAb				X				X				X				X				X
IFNg ELISpot		X				X				X				X				X		
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]	X			X				X				X						X		
Complement Panel	X	X		X				X				X				X				X
Serum for exploratory biomarkers[e]	X	X		X		X		X		X		X				X				X
Exploratory CK18 and Grp78 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	**2[f]**	**3[f]**	**4**	**5[f]**	**6[f]**	**7[f]**	**8**	**9[f]**	**10[f]**	**11[f]**	**12**	**13[f]**	**14[f]**	**15[f]**	**16**	**17[f]**	**18**	**19[f]**	**20**
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
TGA Assay[c]																X				X
Haemo-QOL-A assessment				X								X								
EQ-5D-5L				X								X								
WPAI+CIQ:HS				X								X								
PROBE				X								X								
Testing for reactivation of hepatitis B and hepatitis C						X[g]														X[g]

[*] Visit windows are ± 48 hours.

[a] Brief physical examination should be done at scheduled visits. Additional physical exams may be done at the discretion of the PI.

[b] Refer to Table 9.7.8.2.1for 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 > upper limit of normal (ULN) or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Collection and testing of semen samples must continue at least through Week 12, even if 3 consecutive results below the limit of detection in that compartment have already been recorded.

[e] Blood samples will be collected 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.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

Table 9.1.3: Schedule of Events – Post-Infusion Follow-Up (Weeks 21-52)

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	**22**	**23[f]**	**24**	**25[f]**	**26**	**28**	**30[f]**	**32**	**34[f]**	**36**	**40**	**44**	**48**	**50[f]**	**52**
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Physical examination[a]		X		X		X	X		X		X	X	X	X		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	X	X	X	X
Vital Signs				X		X			X		X	X	X	X		X
Blood chemistry, hematology, and coagulation tests[b]						X			X		X		X			X
Urine Tests[b]						X					X					X
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]						X			X		X		X			X
Immunogenicity AAV5 TAb Assay						X					X					X
AAV5 TI Assay						X					X					X
hFVIII TAb				X		X					X					X
IFNg ELISpot		X		X		X					X					X
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]		X				X	X				X		X			X
Complement Panel				X		X					X					X
Serum for exploratory biomarkers[e]				X		X					X					X
Exploratory CK18 and Grp78 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TGA Assay[e]						X			X		X		X			X

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	22	23[f]	24	25[f]	26	28	30[f]	32	34[f]	36	40	44	48	50[f]	52
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Haemo-QOL-A assessment						X										X
EQ-5D-5L						X										X
WPAI+CIQ:HS						X										X
PROBE						X										X
Testing for reactivation of hepatitis B and hepatitis C									X[g]							
Optional liver biopsy[h]						X										X

[*] Visit windows are ± 48 hours.

[a] Physical examination should be done at all visits. Weight should be recorded at all 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 > ULN or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator.

[e] Blood samples will be collected 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.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

[h] Optional liver biopsy should be obtained within two weeks of Week 26. Additional follow-up liver biopsy will be obtained at Week 52. Subjects should fast for at least 8 hours prior to liver ultrasound and optional liver biopsies.

Table 9.1.4: Schedule of Events-Post-Infusion Follow-Up (Year 2-Year 5)

Assessment	Years 2-5*			End of Year Visit				ETV
	Years 2-5	Year 2	Year 3-5	Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
Physical examination[b]	X			X				X
Weight[b]	X[a]			X[a]				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and hemophilia therapy use)	X	X	X	X				X
Vital Signs	X			X				X
Blood chemistry, hematology, and coagulation tests[c]	X[a]			X[c]				X
Urine Tests[c]	X[a]			X[c]				X
Liver Tests[c]	X	X	X	X				X
hFVIII assays[d]	X	X	X	X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools	(X)[e]			(X)[e]				(X)[e]
Immunogenicity AAV5 TAb Assay				X				X
AAV5 TI Assay				X				X
hFVIII TAb	X			X				X
IFNg ELISpot[a]	X[a]			X				X
Plasma, PBMC, and RBC collection for exploratory biomarkers[f]	X			X				X
Serum for exploratory biomarkers[f]	X			X				X
Exploratory CK18 and Grp78 assessment	X	X	X	X				X
TGA Assay[f]				X				X
Haemo-QoL-A assessment	X[a]			X[a]				X
EQ-5D-5L	X[a]			X[a]				X
WPAI+CIQ:HS	X[a]			X[a]				X

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

* Visit windows are ± 2 weeks for visits in Years 2-5.

[a] These assessments need to be performed only at every other Q12W and every End of Year visit (ie, Weeks 76, 104, 128, 156, 180, 208, 232, and 260).

[b] 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.

[c] 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 > ULN or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

[d] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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.

[e] Sample testing during Years 2-5 is not required if at least 3 consecutive samples were below the limit of detection during Year 1; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Subjects who have not had 3 consecutive semen samples below the limit of detection 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 samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

[f] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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, as well as testing of the TGA assay sample, will be performed only as deemed necessary by the Sponsor.

[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 semen 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. Unscheduled visits may also be conducted by MN as appropriate.

[h] An optional liver biopsy may be performed at any time between Years 2-5 of the study. The optional biopsy would be triggered by a FVIII activity decline by > 50% from steady-state, over 2 consecutive measurements, or by a sustained ALT rise > ULN. If neither triggered is observed, the optional biopsy should be performed at the end of Year 5.

Table 9.1.5: Schedule of Events-Optional Liver Biopsy

	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	Biopsy Day (BD)
Informed Consent for Liver Biopsy Procedure	X		
Liver Ultrasound[a]	X		
Physical examination	X		X
Hematology, Coagulation, Chemistry Assessments[b]	X		X
Liver Tests[b]	X		X
FibroScan	X		
FVIII Activity Level Assessment (central and local)		X	X[*]
Exploratory CK18 and Grp78 assessment		X	X[*]
Pre-Biopsy Consultation[c]		X	
Liver Biopsy[d]			X
PBMC Collection (whole blood draw)			X[e]

[*] If the Day -7 and biopsy day visits occur on the same day, these tests do not need to be duplicated.

[a] Liver ultrasound must be performed within 28 days prior to the scheduled biopsy. Subjects should fast for at least 8 hours prior to liver ultrasound.

[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.

[c] Subjects will undergo a pre-biopsy consultation with the Investigator (treating hematologist) and hepatologist and/or radiologist.

[d] Subjects should fast for at least 8 hours prior to optional liver biopsy. Biopsy will be a percutaneous or transjugular biopsy under ultrasound guidance, performed according to the standard procedure of the institution. If only a small amount of tissue (< 2 cm) is obtained at the time of the biopsy, the subject may be asked to consent for a second pass. In this case, the original < 2 cm sample should still be retained and handled according to the instructions for handling biopsy specimens in the Laboratory Manual. Following completion of the biopsy, the subject should remain in the hospital under observation for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion.

[e] Blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

Table 9.1.6: Suggested Schedule of Events-Prophylactic Corticosteroids

	Corticosteroid Treatment Period[b]																				Post-Corticosteroid Period[c]				
		Week																			Week				
Assessment	**D1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**32**
Prophylactic corticosteroid dose (mg/day)	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	35 mg	35 mg	30 mg	30 mg	25 mg	25 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis B testing[d]							X														X				X
HCV Viral Load[d]							X														X				X

[a] This table provides an example of a prophylactic corticosteroid course. Clinical judgment, weighing the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses, and discussions between the Investigator and Medical Monitor are advised for any questions or concerns. Dosages are for prednisone or an equivalent dose of another corticosteroid. FVIII and liver tests are also reflected in the Schedule of Events for the study.

[b] Following initiation or completion of corticosteroid regimen, if a recurrence of ALT values > ULN or ≥ 1.5x 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, relationship between increases in ALT and FVIII activity, ALT levels/FVIII activity post-corticosteroid initiation, and adverse events related to corticosteroid dosing. Guidance for tapering oral corticosteroid dosing can be found in Section 9.4.8.2, although a discussion between the PI and Medical Monitor should take place prior to tapering the corticosteroid dose.

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

[d] Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry. Tests are also reflected in the Schedule of Events for the study.

9.2 Discussion of Study Design, Including Choice of Control Group

Study 270-303 is a Phase 3b, single arm, open-label study designed to assess whether BMN 270, at a dose of 6E13 vg/kg with prophylactic corticosteroids, can safely and effectively improve the FVIII activity profiles and alter the clinical phenotype of hemophilia A patients with residual FVIII activity ≤ 1 IU/dL. 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a prophylactic corticosteroid regimen. Post-infusion, subjects will be eligible to receive on-demand corticosteroids, as indicated.

9.3 Selection of Study Population

Approximately 20 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 hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
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 viral vector DNA below the limit of detection.
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. Up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the titer level is below the minimum required dilution (< 20).
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. FibroScan or 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.
8. Liver cirrhosis of any etiology as assessed by FibroScan or 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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.
16. 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.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.
19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

9.3.2.1 Optional Liver Biopsy Inclusion and Exclusion Criteria

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

1. Able to sign informed consent and comply with requirements for the optional liver biopsy
2. Documentation of FVIII activity ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII levels activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist/radiologist would make liver biopsy contraindicated. This includes (but is not limited to) abnormalities detected on liver ultrasound performed within 28 days of procedure, or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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. 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 electronic case report form (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, and 260 weeks of post-infusion 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

BMN 270 is a sterile, clear, colorless-to-pale yellow solution for IV infusion and is supplied in a 10 mL Crystal Zenith® (CZ) vial. Each vial contains 8.5 mL (extractable volume 8 mL) of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The IP 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 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.

BMN 270 will be prepared and infused as a pure solution over a dose-dependent time. Prepared drug will be kept at room temperature prior to administration. Refer to the Pharmacy Manual for IP administration instructions.

BMN 270 will be infused through the catheter using an appropriate infusion pump at an initial rate of 1 mL/min. The infusion rate should be increased every 30 minutes by 1 mL/min up to a maximum of 4 mL/min, provided that the subject's clinical condition permits such an increase. Of note, the IP has been shown to be stable at room temperature for 10 hours following completion of product thaw. 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 after an infusion-related reaction. At the restart, the infusion rate may be adjusted (ie, to a slower rate [minimum of 1 mL/min], with the rate increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min, if the subject's clinical condition permits such an increase) with careful monitoring of the subject. In the event of an infusion rate reaction with more than one dosing interruption, the infusion rate would not go beyond 1mL/min.

In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory cytokine bead array (CBA) to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor. Exploratory biomarker samples at baseline and at post-infusion study visits may also be used to assess changes in these biomarkers to better elucidate the mechanisms of infusion-related hypersensitivity reactions. Inpatient 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; inpatient observation can be extended beyond 8 hours if needed per Investigator discretion. After the observation period, subjects will be discharged from the clinic unless toxicity has been observed in which case the stay in the clinic may be extended 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 20 subjects will be enrolled into the single arm study of 6E13 vg/kg with prophylactic corticosteroids. Up to 25% of the total number of patients dosed should have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening.

9.4.6 Selection of Dose Used in the Study

Data from previous human studies (270-201, 270-301) indicated that dosing at 6E13 vg/kg showed improvement in FVIII activity, bleeding episodes, and exogenous FVIII utilization and infusion rate. Dosing was well tolerated, with mild increases in ALT as the most common adverse event. Please refer to the IB for detailed efficacy and safety data.

This dose is expected to be safe and effective based on clinical experience to date in 270-201 and 270-301, as well as non-clinical data.

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 as needed (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
- Fitusiran
- Concizumab
- Efavirenz
- Lamivudine

The following medications and agents 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, including isotretinoin and dextroamphetamine/amphetamine
- Medications which may reduce or increase the plasma concentration of corticosteroids

Subjects should be counseled to avoid starting potentially hepatotoxic therapies and to inform the Investigator of any new medications prescribed by other physicians. Investigators should carefully consider both the mechanism of action and potential hepatotoxicity of any new medication prior to initiation. If a potentially concerning new medication is started, Investigators should closely monitor both FVIII activity and ALT levels (eg, weekly to every 2 weeks for the first month) in order to determine if any detrimental effects on the efficacy or safety of BMN 270 have occurred. If co-medications are required during the course of the study, where possible, please check the National Center for Biotechnology Information LiverTox website for potential hepatotoxicity issues prior to prescribing (NCBI, 2020).

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
- Non-steroidal anti-inflammatory drugs (NSAIDs)

9.4.8.1 Concomitant Hemophilia Treatments

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

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 Investigator 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 Corticosteroid Treatment and/or Alternative Immunosuppressive Agent Treatment of Elevated Hepatic Transaminases

Refer to steroid prescription guidelines to determine eligibility, monitoring and managing of side effects during steroid treatment. Prior to dosing, all subjects must be screened per steroid

prescription guidelines to ensure the subject is eligible to receive corticosteroid treatment as outlined in the protocol. Refer to corticosteroid prescription guidelines for recommended monitoring for, and management of, potential side effects of corticosteroids, including guidance on medications that should be avoided during corticosteroid treatment.

All subjects will be started on prophylactic corticosteroids starting on the day of infusion (Day 1). The first dose of prophylactic corticosteroids (40 mg of prednisone or prednisolone, or an equivalent dose of another corticosteroid) should be taken at least 3 hours prior to the start of the BMN 270 infusion and continued on a daily basis. Table 9.1.6: provides an example of a possible prophylactic corticosteroid course, including taper and post-corticosteroid additional monitoring of FVIII activity, LTs, and hepatitis B/hepatitis C reactivation. Clinical judgment, weighting the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses. Discussions between the Investigator and Medical Monitor are advised for any questions or concerns.

Following initiation or completion of the prophylactic corticosteroid regimen, if ALT levels become increased (eg, ≥ 1.5x baseline value or > ULN) and alternative etiologies have been ruled out, prompt institution of newly administered or an increased dose of therapeutic or on-demand oral corticosteroids (prednisone or an equivalent dose of another corticosteroid) should be considered after consultation with the Medical Monitor (refer to Table 9.7.8.3.2).

- Whenever possible, a confirmatory lab draw for ALT should be performed within 72 hours, along with FVIII activity, prior to initiating oral corticosteroids.
- Newly administered corticosteroids or dose increases are not indicated if elevations in ALT are clearly not related to BMN 270 (eg, elevated ALT with concurrent increase in CPK due to intensive exercise) although this should be discussed with the Medical Monitor.
- Alternative immunosuppressive agents may also be considered for use on a case-by-case basis and following consultation with the Medical Monitor (eg, if prolonged corticosteroid use is contraindicated).

Unless otherwise indicated, therapeutic corticosteroid treatment should be initiated at a dose of 60 mg/day. If the ALT level immediately returns to ≤ 1.5x baseline and FVIII activity levels continue to rise and/or remain within or above the normal range in the 2 weeks following corticosteroid initiation, on-demand corticosteroids can be discontinued. However, if this is not the case, therapeutic corticosteroids should be tapered over a longer period of time. At minimum, the recommended duration of on-demand corticosteroids is 60 mg/day for 3 weeks, 40 mg/day for 4 weeks, and 30 mg/day for 4 weeks, followed by a gradual taper thereafter. Should a scenario arise in which a deviation from the minimum recommended

dose and/or duration of therapeutic corticosteroids may be clinically indicated, a discussion should take place between the Investigator and Medical Monitor regarding corticosteroid dose adjustments. Tapering of corticosteroid dosages should be guided by the following (Table 9.4.8.2.1:):

Table 9.4.8.2.1: Adjustments to Corticosteroid Regimen

Corticosteroids should be tapered on an individual subject basis with the following guiding principles:	Corticosteroids may be tapered **if**: • ALT ≤ 1.5x baseline value; and • FVIII activity levels > 90% of the pre-decline FVIII activity levels; and • There is no concern for adrenal insufficiency post-withdrawal
Increasing Corticosteroid Dose	If ALT level is increasing or FVIII activity 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 on-demand 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 increased ALT levels (eg, > ULN or ≥ 1.5x baseline value) are 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 SoA. 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.). Alternative, non-steroidal systemic immunosuppressive agents may be used, following a discussion between the Investigator and the Medical Monitor, should corticosteroid use be deemed by an Investigator to be clinically ineffective, not tolerated, and/or contraindicated. Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of oral corticosteroid/immunosuppressive agent treatment and then 1 week and 13 weeks after the completion of oral corticosteroid/immunosuppressive agent 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/immunosuppressive agent use) should be reported as outlined in Section 10 of the protocol.

Subjects on corticosteroids should receive appropriate counselling and support regarding side effects from the Investigator or the treating institution (eg, listings of side effects and when to notify carers, wallet card for emergencies if on steroids, etc.). Additional management, including the co-prescription of additional medications to prevent complications related to corticosteroid therapy, may be undertaken at the discretion of the investigator, including, but not limited to, prophylaxis against the occurrence of gastric ulcers, osteoporosis, and infections. The above guidance should also be followed in the event that an alternative immunosuppressive agent is used, as applicable.

9.4.9 Treatment Compliance

IP 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 IP containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP 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 standard operating procedures (SOPs).

9.5.1 Return and Disposition of Clinical Supplies

Unused IP 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 IP or study materials (or must be referenced in their institution SOPs).

Unused IP may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The study monitor must account for all IP in a formal reconciliation process prior to IP destruction. All IP 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 IP appropriately, the site can return unused IP to BioMarin upon request. The return of IP or IP materials must be accounted for on a IP return form provided by BioMarin.

All IP 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 starting at the time of informed consent for study participation and for the first 52 weeks of the study, and particularly within 48 hours prior to lab work. Alcohol use should be minimized throughout the remaining duration of the study.

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 blood and semen samples, respectively. Subjects should also abstain from organ donation.

9.7 Safety and Efficacy Variables

9.7.1 Safety and Efficacy Measurements Assessed

The Schedule of Events (Table 9.1.1 through Table 9.1.4:) 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.

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 the end of 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.

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 include:

- Change in the annualized utilization (IU/kg/year) and infusion (number/year) rates of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion from the baseline number and utilization of exogenous FVIII replacement therapy, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change in administration of exogenous FVIII replacement therapy Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis.
- Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) during Week 5 to Week 52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis, from the baseline ABR during the 12 months prior to study entry.

Subjects must have high quality documented historical data available concerning previous bleeding episodes and hemophilia treatment 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 or use of emicizumab.

9.7.3.2 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).

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.

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).

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).

Details (including sample copies where applicable) for each of the PRO instruments are provided in the Investigator Site File Binder.

9.7.4 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 chromogenic 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.

9.7.5 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.

9.7.6 Pharmacokinetics

Sparse FVIII activity assessments, prior to BMN 270 administration, will be collected to estimate each subject's half-life of replacement FVIII concentrate used for prophylaxis. Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. If supported by the data, sparse samples together with established population pharmacokinetic models will be used to estimate an individual subject's FVIII activity clearance (CL) value. Individual subject CL estimates may then be evaluated against post-BMN 270 FVIII activity levels to determine if an association exists between an individual's FVIII activity CL value and FVIII activity levels achieved with BMN 270. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

9.7.7 Exploratory Assessments

Blood samples will be collected from subjects at the time points indicated in the Schedules of Events 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.

9.7.7.1 Optional Liver Biopsy

Subjects electing to undergo an optional liver biopsy are required to consent to the procedure and collection of tissue in the study ICF. The analysis of the optional liver biopsy is considered exploratory. Patients who elect to proceed will have a liver biopsy performed around Week 26, Week 52, and/or during Years 2-5. Additional liver biopsies at times deemed to be clinically relevant (eg, decreasing FVIII at a time of increased ALT) may be

pursued. Subjects will be asked to consent to the procedure for each liver biopsy performed during the study.

Subjects who consent to the procedure will have a liver biopsy via either transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. Two tissue cores will be harvested in the context of the optional liver biopsy. Subjects will be required to observe an 8-hour fasting period before the procedure.

Within 24 hours prior to the biopsy being performed, subjects must have a documented FVIII activity level of ≥ 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). FVIII activity levels for this purpose should be assessed at the local laboratory within 7 days before the biopsy and again on the day the biopsy, prior to the procedure. As needed, subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity levels to an appropriate level, under the supervision/instruction of the investigator, to ensure the safety of the subject during the procedure. This exogenous FVIII usage (if performed) should be recorded in the eCRF FVIII infusion pages under the category “Surgery/Procedure”.

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5. Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests
- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- Local FVIII activity level assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion and/or according to local guidelines.

Clinically significant findings reported from the histopathological analysis of the biopsy sample are subject to AE reporting (Section 10). Such findings should be further assessed and followed as clinically appropriate to manage the subject's medical care. A hepatologist and/or other specialist clinicians should be consulted if required. In the event that fibrotic changes are observed on the biopsy sample, additional liver ultrasound, FibroScan and/or Enhanced Liver Fibrosis (ELF) testing (as regionally available and/or approved by HA) may be considered at the discretion of the investigator and/or hepatologist.

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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

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.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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	**Other Tests:**
CRP		Bilirubin	ABO blood typing*
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 at Screening.

In addition to scheduled clinical laboratory assessments, a fasting blood lipid panel (including triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) and

FibroTest 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory CBA to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

At applicable sites, certain study assessments may be performed by an 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 at the visits indicated in the Schedules of Events. Unscheduled visits may also be conducted by MN as appropriate.

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 negative surface antigen or DNA for hepatitis B or negative 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 the timepoints listed in Table 9.1.6. 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.

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

LTs 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
≥1.5x Baseline - <2x Baseline	• Continue to monitor LTs and FVIII per protocol (repeat within 24-72 hours if next protocol scheduled visit is >24-72 hours 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 or > 2x baseline in 2 consecutive assessments within 24-72 hours and alternative etiologies have been ruled out, start oral corticosteroids upon consultation with the Medical Monitor (refer to Section 9.4.8.2) • Consider liver biopsy at the discretion of the Investigator or Medical Monitor
≥2x Baseline or > ULN - <3x ULN	• Repeat LTs and FVIII within 24-72 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 ≥ 2x baseline or > ULN - < 3x ULN 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) • 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
≥3x ULN	• Consult with Medical Monitor • Evaluate and rule out alternative etiologies (as above) • Repeat LTs and FVIII within 24-48 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 the timepoints indicated in the schedules of events. 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 should be performed during Screening/Baseline, at Week 26 (± 2 weeks) 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.

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 at the timepoints indicated in the Schedules of Assessments.

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. Testing will continue until at least 3 consecutive results below the limit of detection are obtained; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive semen samples below the limit of detection by Week 52 should continue to have PCR testing in semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

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, stool). 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, after consultation between the Medical Monitor and the Investigator, 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 below the limit of detection for vector DNA on at least three consecutive visits.

Contraception use may need to be extended beyond 12 weeks in individual subjects based on observed vector shedding in semen. After 12 weeks, subjects may stop contraception use only if they have had 3 consecutive semen samples below the limit of detection (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.

  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 > ULN or > 1.5x baseline value, regardless of whether that elevation triggers an initiation or modification of oral corticosteroid treatment
- Thromboembolic event
- Immediate reactions: infusion-related reactions, hypersensitivity adverse events, or anaphylaxis
- 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 Common Terminology Criteria for Adverse Events (NCI CTCAE) v5. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5as 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/or corticosteroids and/or other immunosuppressant agents 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 and/or corticosteroids has not occurred **OR** • The administration of the IP and/or corticosteroids 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 and/or corticosteroids; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP and/or corticosteroids.
Related	• The administration of the IP and/or corticosteroids 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 and/or corticosteroids **OR**
	• The administration of IP and/or corticosteroids and the occurrence of the AE are reasonably related in time **AND** • The AE is more likely explained by exposure to the IP and/or corticosteroids 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 and/or corticosteroid exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug and/or corticosteroid action
- Similarity to adverse reactions seen with related drug products
- Abatement of AE with discontinuation of study drug and/or corticosteroids, and/or recurrence of AE with reintroduction of study drug and/or corticosteroids

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, unless the abnormal laboratory results has been reported or captured as part of an underlying diagnosis.

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 BioMarin Pharmacovigilance (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 electronic data capture (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 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: PI
Fax: PI
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: PI , MD, MHS
Address: 105 Digital Drive
Novato, CA 94949 USA
Phone: PI
E-mail: PI

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.

During the first part of the Screening Period (Day -42 to Day -29), testing for AAV5 TAb titers using the CDx screening assay may be performed, so that subjects can verify their AAV5 TAb status. Subjects who agree to participate in this activity may be asked to sign a separate ICF documenting this decision. Subjects who do not have testing during this period will have CDx AAV5 TAb testing along with the rest of the Screening assessments.

If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

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 hemophilia 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 Investigator Site File Binder.
- Distribution of subject diaries and training in diary completion
- Electrocardiogram
- Liver ultrasound/FibroScan
- 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)
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - hFVIII protein assay (collected but not tested prior to enrollment)
- hFVIII total antibody (TAb) assay (collected but not tested prior to enrollment)
- 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)
    - ABO blood typing assessment should be performed at Screening
- Urine tests (refer to Table 9.7.8.2.1)
- Liver tests (refer to Table 9.7.8.3.1)
- AAV5 TAb Assessment (CDx)
    - If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening
- Biomarker testing (including HLA genotyping and FVIII genotyping status)
- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment

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))
- 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)
- AAV5 TAb Assessment (CDx)

12.3 Baseline Visit

Baseline values will be recorded from 1 to 7 days prior to the treatment visit. Subjects are considered enrolled into the study once the Baseline visit has occurred. 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)
- 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
  - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
  - hFVIII protein assay
- hFVIII TAb
- 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)
- Immunogenicity AAV5 TAb assay
- AAV5 TI assay
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Complement Panel
- Exploratory CK18 and Grp78 assessment
- TGA Assay
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Pharmacokinetics
  - Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional

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:

- Initiation of prophylactic corticosteroids (at least 3 hours prior to BMN 270 infusion)
- Brief physical examination

- 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.
- Assessment of adverse events and concomitant medications
- 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.
- Fasting FibroTest
- AAV5 TAb Assay (CDx) (sample collected pre-infusion for analysis)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- Serum for exploratory biomarkers
- BMN 270 Infusion
- Hypersensitivity blood assessments (if required, see below)
- 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory CBA to assess inflammatory biomarkers and plasma cytokine levels. Inpatient 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 have weekly assessments during Weeks 1-26. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At the Week 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:

- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- Exploratory CK18 and Grp78 assessment

12.5.2 Week 1 - Day 8

On Day 8, the following procedures will be performed, in addition to the weekly assessments required in Section 0:

- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Complement Panel

12.5.3 Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 26

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

- Serum for exploratory biomarkers

12.5.4 Weeks 2, 4, 8, 12, 16, 20, 24, and 26

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

- Complement Panel

12.5.5 Weeks 2, 6, 10, 14, 18, 22, 24, and 26

At Weeks 2, 6, 10, 14, 18, 22, 24, and 26, the following procedure will be performed:

- IFNg ELISpot

12.5.6 Weeks 4, 8, 12, 16, 20, 24, and 26

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

- Vital Signs
- Weight (not done at Week 24)
- hFVIII TAb
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not done at Week 24)
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained. Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point.

12.5.7 Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26

At Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26, the following procedures will be performed:

- Brief physical examination
    - A complete physical examination should be done at Week 26.

12.5.8 Weeks 4, 8, 16, and 26

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

- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay

12.5.9 Weeks 4, 8, 12, 18, 22, and 26

At Weeks 4, 8, 12, 18, 22, and 26, the following procedure will be performed:

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.5.10Week 4, 12, and 26

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

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

12.5.11 Weeks 4, 16, and 26

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

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

12.5.12 Weeks 12 and 26

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

- Urine Tests (refer to Table 9.7.8.2.1)

12.5.13 Weeks 16, 20, and 26

At Weeks 16, 20, and 26, the following procedure will be performed:

- TGA Assay

12.5.14 Weeks 6 and 20

At Weeks 6 and 20, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

12.5.15 Week 26

At Week 26, the following optional procedure will be performed:

- Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)

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

After Week 27, subjects will have assessments at Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At these visits, the following assessments will be performed.

12.6.1 Each Visit (Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52)

The following procedures will be performed at every visit (Week 26, 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52):

- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- Exploratory CK18 and Grp78 assessment

12.6.2 Weeks 28, 32, 36, 40, 44, 48, and 52

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

- Brief physical examination (complete physical examination at Week 52)

12.6.3 Week 28, 36, 44, and 52

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

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.6.4 Week 32

At Week 32, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

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

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

- Vital Signs

12.6.6 Weeks 32, 36, 44, and 52

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

- Weight
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained.
- TGA 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)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- hFVIII TAb
- IFNg ELISpot
- Complement Panel
- Serum for exploratory biomarkers

12.6.8 Week 52

At Week 52, the following procedure will be performed:

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

12.6.9 Week 52

At Week 52, the following optional procedure will be performed:

- Optional liver biopsy (refer to Section12.9 for assessments related to liver biopsy)

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 and Q6W visits during Years 2-5; 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. Unscheduled visits may also be conducted by MN as appropriate.

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 semen 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.

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

12.7.1 Year 2 (Every 4 Weeks) or Years 3-5 (Every 6 Weeks)

During Years 2 (every 4 weeks ±2 weeks) or 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
        - If a subject tests positive in the cNBA 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
- Exploratory CK18 and Grp78 assessment

12.7.2 Years 2-5 – Every 12 Weeks and End of Year Visits

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 (final study visit)

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.

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)
- Vital Signs
- 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)
- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
        - If a subject tests positive in the cNBA 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
- Immunogenicity AAV5 TAb Assay (at End of Year visits only)
- AAV5 TI Assay (at End of Year visits only)
- hFVIII TAb
- Interferon gamma (IFNg) ELISpot (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers

- Exploratory CK18 and Grp78 assessment
- TGA Assay (at End of Year visits only)
- 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)
- 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)
- 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 below the limit of detection during the Post-Infusion Follow-Up period in Weeks 1-52. Subjects who have not had 3 consecutive semen samples below the limit of detection 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 samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).
- Optional liver biopsy (Years 2-5) (refer to Section 12.9 for assessments related to liver biopsy)

12.8 Early Termination 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 ETV. The Early Termination Visit (ETV) will occur on the date the subject withdraws from the study, even if the date does not correspond to a protocol-specific visit. At the ETV, as many of the following assessments as possible should be done:

- Complete 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- hFVIII TAb
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment
- TGA Assay
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE

12.9 Optional Liver Biopsy

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5. Subjects may be asked to provide a liver biopsy around Week 26, Week 52, and during the Years 2-5 period post-BMN 270 infusion.

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- FVIII activity level assessment (central and local)
- Exploratory CK18 and Grp78 assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion and/or according to local guidelines.

12.10 End of Study

The study will end after the last subject yet to complete the Week 260 visit 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.

Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

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 analyses. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

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.

Missing data imputation and sensitivity analyses to assess the impact of missing data on the primary and secondary efficacy endpoints analyses are described in the following sections. 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 at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels ≤ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose hFVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 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 14.9.

14.3 Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion:

- Change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment during Weeks 5-52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Weeks 27-52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

The missing value of the change for annualized utilization and annualized infusion rate will be imputed as 0. The missing value of the change for annualized number of bleeding episodes will be imputed using the median value of the changes of all observed cases.

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, repeated within subject. The actual number of bleeding episodes will be used as the dependent variable with the time period adjustment (annualization) 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.

14.4 Tertiary Efficacy Endpoints

The analyses of the tertiary efficacy endpoints will be descriptive. Mean change from baseline and associated 95% confidence interval will be provided for EQ-5D-5L, WPAI+CIQ: HS and PROBE scores at Week 52 post-BMN 270 infusion.

14.5 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.

14.6 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).

14.7 Safety Analysis

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

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.

14.8 Determination of Sample Size

Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects who have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening.
For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or

equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

14.9 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

Subjects with an AAV5 antibody titer detectable but below the minimum required dilution will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post BMN 270 infusion.

14.10 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 must be sought, and the Investigator should inform BioMarin and the full IRB/IEC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC 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 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, 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 continue enrolling subjects based on emerging data and the overall risk/benefit analysis of BMN 270.
- Making other recommendations on the conduct and reporting of the trial based on their evaluation of clinical data.

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 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 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 date and 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. 1995;19:1409-1417.

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

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. 2012;18(Suppl.6):1-13.

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.

Grant A, Neuberger J, Day C, Saxseena S. British Society of Gastroenterology Guidelines on the use of Liver Biopsy in Clinical Practice. 2004. Available at: https://www.bsg.org.uk/resource/bsg-guidelines-on-the-use-of-liver-biopsy-in-clinical-practice.html (last visited 20 January 2020).

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

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

Iorio A, Stonebraker JS, Chambost H, et al, for the Data and Demographics Committee of the World Federation of Hemophilia. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-546.

Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia 1. Blood. 2013;122(22):3568-3574.

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. 2014;371(21):1994-2004.

National Center for Biotechnology Information (NCBI). LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Available at: https://livertox.nih.gov (last accessed 14 January 2020).

National Hemophilia Foundation. MASAC recommendation for liver biopsies in gene therapy trials for hemophilia. Available at https://www.hemophilia.org/sites/default/files/document/files/256.pdf. 2019. MASAC Recommendation #256. Last accessed 18 December 2019.

Pasi KJ, Rangarajan S, Mitchell N, Lester W et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med. 2020;382(1):29-40.

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. 2013;19(1):e1-47.

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

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 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. Additionally, he or she will not make any changes in the research without IRB/EC 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 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

Protocol Number: 270-303

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:

PI PI

PI Signature Date

Printed name: PI MD, MHS, PI , Clinical Sciences

24 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):

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

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

Source: Sampson, 2006.

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients
Protocol Number:	270-303
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	IND #: 017659 2018-004616-21
Indication:	Hemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3b
Sponsor's Responsible Medical Monitor:	PI , MD, MHS PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	6E13 vg/kg
Study Population:	Males aged 18 or older
Date of Original Protocol:	28 February 2020
Date of Amendment 1:	15 September 2020

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment 1

Date: 15 September 2020

RATIONALE AND SUMMARY OF CHANGES

A summary of major changes covered by Amendment 1 to the 270-303 protocol is provided below:

1. Screening testing for COVID-19 has been added.

Rationale: Exclusion criteria for the study already included a provision excluding subjects with an active infection. In light of the emergence of the novel coronavirus SARS-CoV-2, the criterion has been modified to specify that this includes testing for active COVID-19 infection, which has been added to the Screening visit in the Schedule of Activities.

2. The occurrence of events of Hy's law has been added as an event of special interest (EOSI) for purposes of expedited safety reporting, and additional safety monitoring in the event of a case potentially meeting Hy's law criteria has been added.

Rationale: Events potentially meeting the criteria for Hy's law involve combined assessment of elevations in aminotransferases and total bilirubin levels, while the current list of EOSI focuses on elevations in aminotransferases. To date, no events meeting the criteria for Hy's law have been reported in any BMN 270 study. While monitoring for events of Hy's law has been ongoing as part of routine pharmacovigilance in all BMN 270 studies, this change ensures that the occurrence of any events in the future will be reported in an expedited manner. In addition, expanded laboratory monitoring (to include albumin and PT/INR) has been added to the guidelines for evaluating potential Hy's law cases.

3. Language has been added concerning the use of liver biopsy sample information for biopsies performed for safety-related reasons.

Rationale: Where a biopsy has been taken for safety-related reasons or was available from a past procedure, the Sponsor may want to see that biopsy information to help evaluate the impact of BMN 270 on the liver. The Sponsor may request that slides from a liver biopsy be made available for additional histopathological review.

4. Clarifying language has been provided for circumstances where a positive vector shedding sample occurs after 3 consecutive tests below the limit of detection have already been obtained.

Rationale: The protocol did not previously specify whether testing should be restarted after a positive result occurs after 3 consecutive results below the limit of detection in a matrix have

been obtained. While this situation would be expected to be rare, and usually subjects remain below the limit of detection after having achieved 3 results below the limit of detection in a row, in the instance where a positive test occurs then testing should restart and continue until an additional 3 consecutive results below the limit of detection have been obtained. The purpose of the testing is to declare vector clearance, and in the instance where a positive test occurs even after 3 tests below the limit of detection, clearance cannot be confirmed without further testing.

5. An optional monthly phone check-in has been added during Years 2-5 for subjects who are returning to the site only every 12 weeks due to poor FVIII response following BMN 270 infusion.

Rationale: To ensure timely safety monitoring and promote subject retention, subjects who are not attending the Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

6. The option to assess an adverse event as related/not related to other systemic immunosuppressive agents has been added.

Rationale: AEs associated with other systemic immunosuppressive agents (if used) are possible and should be noted as such on the eCRF (and for safety monitoring and risk:benefit assessment purposes).

7. Lamivudine has been removed as a prohibited medication.

Rationale: Lamivudine was added as a prohibited medication after an HIV-positive subject in a BMN 270 study developed severe ALT elevations while receiving anti-retroviral therapy that included lamivudine as one of its components (and out of concern that lamivudine might be interacting with BMN 270 to exacerbate ALT elevations). However, after discussion with a liver health advisory board, lamivudine is not viewed as a likely medication that would interact with BMN 270 and, as such, should no longer be listed as a prohibited medication.

8. The requirements around the use of mobile nursing (MN) services to conduct unscheduled visits for assessment of FVIII levels or liver tests (LTs) have been clarified.

Rationale: In instances where a subject's LTs have been elevated, assessment and workup of those elevations may require additional laboratory work (FVIII and LT levels) to be collected at unscheduled visits. At sites where MN services have been approved, these unscheduled laboratory tests may be performed by a MN professional, rather than requiring a site visit.

9. The header to Section 9.2 (Discussion of Study Design, Including Choice of Control Group) has been modified to remove reference to a control group.

Rationale: Given that BMN 270 is likely a one-time treatment, due to antibody formation against the AAV5 capsid post-infusion, and the well-characterized clinical experience of patients with severe hemophilia A on currently available chronic therapies, having a separate control group in this study was deemed to be inappropriate and unnecessary, as has been the case with all AAV gene therapy trials to date.

10. Guidance concerning how to determine whether a subject has been lost to follow-up has been added.
11. The costs and compensation language has been updated to clarify which study-related costs will be covered by the Sponsor.
12. Complement panel testing has been added to Day 1 to provide a sample closer in time to the BMN 270 infusion.
13. The summary of risks and benefits has been updated to reflect more current clinical results.
14. The required timepoints for vector shedding sample collection during Years 2-5 (if required) have been clarified.
15. Additional minor changes have been made for consistency and clarity.

Refer to Section 25 for a summary of revisions to the original protocol (dated 28 February 2020).

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 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients		
PROTOCOL NUMBER: 270-303		
STUDY SITES: Approximately 10 sites worldwide.		
PHASE OF DEVELOPMENT: Phase 3b		
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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 includes 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 and/or subcutaneous injection of a bi-specific monoclonal antibody, emicizumab, as prophylaxis 1-4 times per month. 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 annualized bleeding rate [ABR] of 1-4 with prophylaxis treatment in a recently published retrospective observational study 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 and between 20-60 in		

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 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. While emicizumab prophylaxis has yielded lower bleed rates compared to prior FVIII prophylaxis, it does not physiologically recapitulate the coagulation system, requires chronic, life-long therapy, and still necessitates the use of on-demand FVIII concentrates for treatment of breakthrough bleeds. 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.

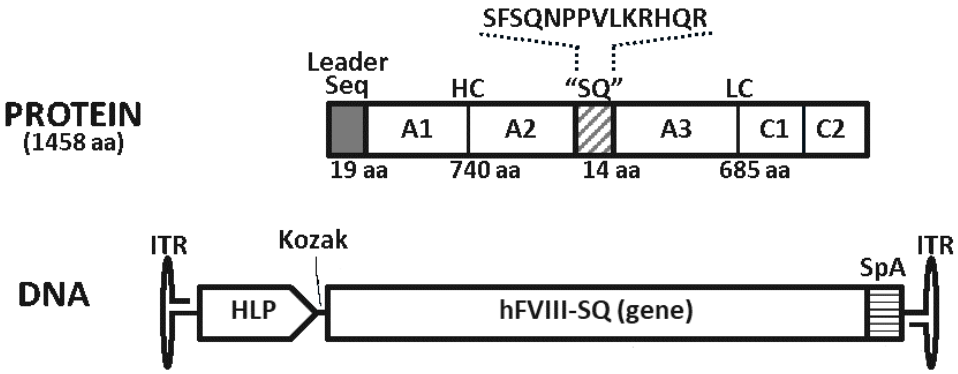
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. HA is well-suited for a gene replacement approach because clinical 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 6.7 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.

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 and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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 vector genomes [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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive).

Three-year results from 270-201 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile. Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm pan-lobular and otherwise healthy liver transduction at 2.5 years. In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201.

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 receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were started on corticosteroids by Week 3 (either therapeutically, in response to an ALT elevation, or prophylactically), whereas in 270-301 subjects received corticosteroids only in response to an alanine aminotransferase (ALT) elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion, showed later advent of first ALT elevations, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation when compared with subjects in 270-301 (20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity. Recently published data from 270-201 suggests that corticosteroids may have assisted in rescue or protection of FVIII levels during elevations of ALT and in resolution of elevated ALT levels in some subjects.

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

OBJECTIVES:

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

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:**

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

The safety objectives of the study are to:

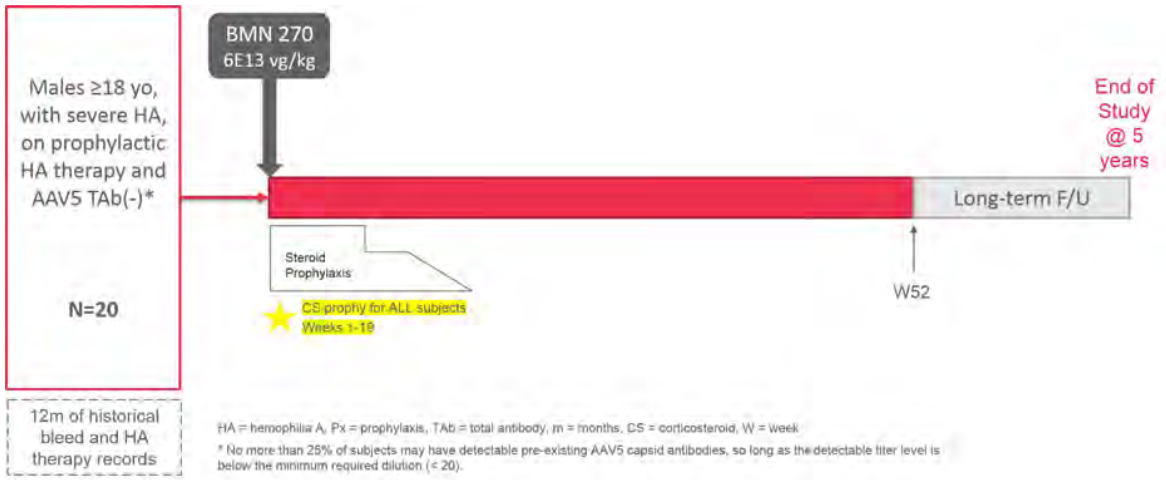
- Evaluate the safety of BMN 270 with prophylactic corticosteroids during the first 52 weeks following intravenous infusion of BMN 270
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

STUDY DESIGN AND PLAN:

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 10 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of BMN 270 infusion (Figure 2). Therapeutic corticosteroids, as needed for ALT elevations and/or FVIII decline, will also be available post-infusion.

Figure 2: 270-303 Study Schema



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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Patients will receive prophylactic corticosteroids with

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:

tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and consultation with the Investigator and the Medical Monitor. Therapeutic oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

Additionally, 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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

NUMBER OF SUBJECTS PLANNED:

Approximately 20 subjects will be enrolled into the study, with at least 16 AAV5 TAb-negative and up to 25% AAV5 total antibodies (TAb) detectable but below the minimum required dilution.

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.

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:

2. Must have been on prophylactic hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
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 viral vector DNA below the limit of detection.
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. Up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the detectable titer level is below the minimum required dilution (< 20).
2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, including HIV infection.
3. Significant liver dysfunction with any of the following abnormal laboratory results:
   - ALT (alanine aminotransferase) > 1.25x upper limit of normal (ULN);
   - AST (aspartate aminotransferase) > 1.25x ULN;
   - GGT (gamma-glutamyltransferase) > 1.25x ULN;

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:

- 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. Most recent, prior FibroScan or liver biopsy showing significant fibrosis of 3 or 4 as rated on a scale of 0-4 on the Batts-Ludwig or METAVIR 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.
8. Liver cirrhosis of any etiology as assessed by liver ultrasound/FibroScan.
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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.

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:

16. 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 corticosteroid treatment and/or the use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.
19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

<u>Optional Liver Biopsy Inclusion and Exclusion Criteria</u>

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

1. Able to sign informed consent and comply with requirements for the optional liver biopsy
2. Documentation of FVIII activity level ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist or radiologist, would make liver biopsy contraindicated. This includes (but is not limited to): abnormalities detected on liver ultrasound performed within 28 days of procedure or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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 6E13 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 from baseline in the annualized utilization (IU/kg/year) and infusion rate (number/year) of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis.
- Change from baseline in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) during Week 5 to Week 52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the total score of Haemo-QoL-A at Week 52 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:

Tertiary efficacy endpoints:

- Change from baseline in the EQ-5D-5L score at Week 52 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 post-BMN 270 infusion.
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 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, stool, saliva)
- Liver tests (LTs, including ALT, AST, GGT, lactate dehydrogenase [LDH], total bilirubin, and alkaline phosphatase)
    - 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.
- Immune response to FVIII transgene product and AAV5 capsid proteins
- Immunological assessments, including hFVIII TAb, interferon gamma (IFNg) ELISpot, complement, and an exploratory biomarker panel.

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.

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:

STATISTICAL METHODS:

Sample Size

Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects who have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening.

For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

Analysis Population

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

Subjects with an AAV5 antibody titer detectable but below the minimum required dilution will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post-BMN 270 infusion.

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. Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels $\leq$ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose FVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 IU/dL, and the confidence intervals of the proportions will also be provided.

The analyses of the secondary and tertiary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to 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 the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment during Weeks 5-52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Weeks 27-52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis from baseline

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

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.

The final analysis for the study will be performed after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52).

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

Details of the planned analyses will be specified in the SAP.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAV	adeno-associated virus
ABR	annualized bleeding rate
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CBA	cytokine bead array
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CL	clearance
cNBA	FVIII chromogenic Nijmegen Bethesda Assay
CRA	clinical research associate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
ED	exposure days
EDC	electronic data capture
EMA	European Medicines Agency
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	hemophilia A
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
HLP	hybrid human liver-specific promoter
IB	investigator's 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
IFNg	interferon gamma
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MN	mobile nursing
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
PRO	patient-reported outcome
PROBE	Patient Reported Outcomes, Burdens, and Experiences
rhFVIII	recombinant human FVIII
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SOI	Statement of Investigator
SOP	standard operating procedure
SQ	SFSQNPPVLKRHQR

SUSAR	serious unexpected suspected adverse reactions
TAb	total antibody
TGA	thrombin generation assay
TI	transduction inhibitor
ULN	upper limit of normal
vg	vector genomes
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) 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 will be provided to BioMarin or its designee. The Investigator will provide the IRB/IEC 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 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 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 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 ICF, in compliance with ICH E6 (Section 4.8), 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. BioMarin and the IRB/IEC 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 (Iorio, 2019). 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 hybrid human liver-specific transcription promoter (HLP). 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 intravenous (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 European Medicines Agency (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

Ongoing clinical studies for BMN 270 include:

- 270-201, a phase 1/2, dose-escalation study in patients with severe HA
- 270-203, a phase 2 study in patients with severe HA who have anti-AAV5 antibody titers
- 270-301, a phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 vector genomes [vg]/kg dose level
- 270-302, a phase 3 study in patients with severe HA who receive BMN 270 at the 4E13 vg/kg dose level

A comprehensive review of safety, efficacy, and immunogenicity results from these studies 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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 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.

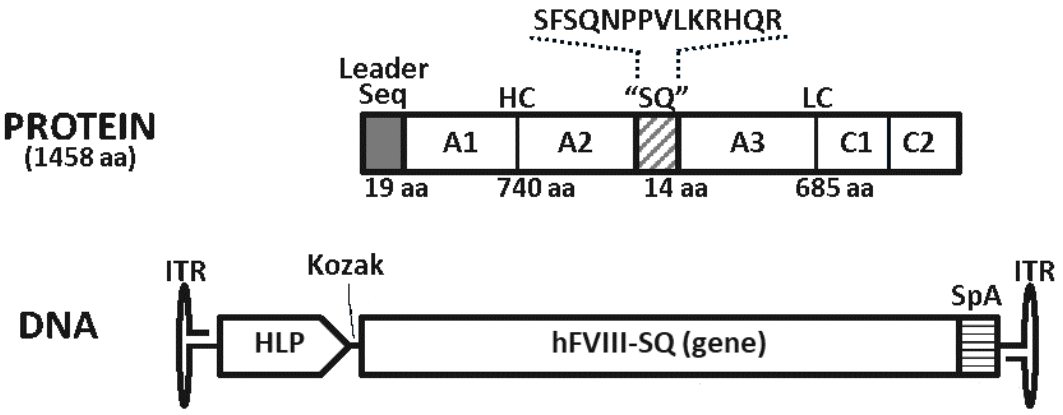
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. Hemophilia A is well-suited for a gene replacement approach 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 6.7years; Nathwani, 2018) 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 and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with

severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive). With the exception of 270-203, subjects in other BMN 270 studies who are AAV5-antibody positive have been excluded. In 270-303, up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the detectable titer level is below the minimum required dilution (< 20). It is expected that subjects with such a low detectable titer level will respond in a similar manner to subjects who are AAV5 capsid antibody negative.

Three-year results from 270-201 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile (Pasi, 2020). Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm pan-lobular and otherwise healthy liver transduction at 2.5 years. In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201 (Pasi, 2020).

Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were started on corticosteroids by Week 3 (either therapeutically, in response to an alanine aminotransferase [ALT] elevation, or prophylactically), whereas in 270-301 subjects received corticosteroids only in response to an ALT elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion, showed later advent of first ALT elevations, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation when compared with subjects in 270-301 (20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity. Recently published data from 270-201 suggests that corticosteroids may have assisted in rescue or protection of FVIII levels during elevations of ALT and in resolution of elevated ALT levels in some subjects (Pasi, 2020).

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

7.3.1 Optional Liver Biopsy Rationale

The usual pattern of response in hFVIII activity observed so far after administration of BMN 270 demonstrates peak expression levels during the first 6-12 months post-treatment followed by a decline to a steady-state level of expression thereafter. One of the explanations may lie in the kinetics of vector genome processing, which involves a series of steps such as DNA degradation and repair, annealing, and circularization that can result in the formation of stable, double-stranded, circularized transgene DNA forms. It is these circularized DNA species that are thought to be associated with long-term, persistent expression of the gene product in target cells. Examination of transduced hepatocytes from subjects treated with BMN 270 in the 270-303 study will help to establish whether DNA circularization may occur and could account for the long-term hFVIII expression observed in humans.

Additionally, health of the liver after gene transduction has been monitored indirectly by periodic assessments of hepatic enzymes released into the blood stream. Transient, post-treatment elevations in ALT levels have been observed in the majority of subjects, as well as inter-subject variability in post-therapy FVIII activity levels. Neither the reasons for nor the significance of the ALT elevations or the variations in response to FVIII gene therapy are known. Moreover, the effects of BMN 270 on hepatic tissue structure and function are also currently unknown. Finally, a call to incorporate liver biopsy sub-studies into gene therapy trials for hemophilia has been issued by medical and scientific leaders in the field to help illuminate these and other questions (National Hemophilia Foundation, 2019).

The purpose of this exploratory sub-study is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in FVIII activity levels observed after gene therapy with BMN 270. With use of prophylactic corticosteroids, it is believed that there will be stable hepatic function and FVIII activity expression, with tolerance of prophylactic corticosteroid therapy and no change to the risk of thromboembolism. This sub-study aims to evaluate the effect on the liver by performing liver biopsies at approximately Week 26, Week 52, and/or during Years 2-5.

7.4 Summary of Overall Risks and Benefits

Overall, 151 subjects have received a BMN 270 infusion at one of 4 dose levels (6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, or 6E13 vg/kg) in one of the four ongoing BMN 270 clinical studies (270-201, 270-301, 270-302, 270-203). Single infusions have been generally well tolerated by treated subjects across all investigated doses. All subjects have successfully completed their full-dose infusion of BMN 270, with no infusions requiring permanent termination prior to completion due to AEs. No deaths have been reported in any of the

BMN 270 studies, and no participants discontinued from studies as a result of an AE. Frequency of adverse events decreased over time with no delayed adverse drug reactions.

Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) has been observed in most subjects administered BMN 270 shortly after dosing, with no symptoms or sequelae suggestive of clinically significant hepatocyte injury or liver dysfunction; no events meeting the Hy's Law criteria have been identified. ALT elevations have been reported as events of interest in 13 subjects in 270-201, 1 subject in 270-302, and 91 subjects in 270-301. Although the majority of events have been Grade 1 or Grade 2 in severity, 11 subjects (1 in 270-302 and 10 in 270-301) had a reported Grade 3 ALT elevation. Only one serious event of ALT increased has been reported by investigators (in addition to one event that BioMarin conservatively assessed as serious based on the details of the case). While the majority of ALT elevations responded rapidly to corticosteroids, given current interest in the field of AAV gene therapy for the use of non-steroidal approaches to managing or preventing ALT elevations, alternate non-steroidal systemic immunosuppressive agents have also been used to manage hepatic reactions where corticosteroids have proven to be ineffective or where high doses/and or prolonged exposure to corticosteroids have led to unwanted side effects. Overall, the literature and clinical experience with BMN 270 suggests that transient elevations in liver enzymes are expected following AAV-based gene therapy for the treatment for hemophilia A or B without any long-term concerns of hepatic injury (Manno, 2006; Nathwani, 2011; George, 2016; Miesbach, 2016; Pasi, 2017).

Short-lived infusion reactions associated with one-time BMN 270 administration have included symptoms such as nausea, maculopapular rash, urticaria, diarrhea, watery eyes, rigors, chills, myalgia, fever, tachycardia and hypotension emerging within 24 hours of receiving BMN 270. Most infusion-related reactions were Grade 1 or Grade 2 in severity, and all events resolved, typically within 48 hours following medical management. Three of these cases required temporary interruption of the infusion, followed by re-initiation at a slower rate. All subjects completed their infusions. The reactions with onset during or within approximately 5 hours after the end of infusion responded to treatment with systemic antihistamines and/or corticosteroids, where administered. Infusion-related reactions were effectively mitigated by managing infusion rate and medications.

No subjects have experienced thromboembolic events or developed inhibitors to FVIII following BMN 270 infusion.

In this study, corticosteroids will be initiated prophylactically (ie, prior to any increase in ALT) on Day 1, prior to the BMN 270 infusion. Close monitoring of ALT and FVIII activity is recommended to enable early and timely initiation of therapeutic corticosteroid treatment

(ie, in response to an increase in ALT). During prophylactic and therapeutic corticosteroid treatment, emphasis will be placed on a slow taper of the dose, with the aim of achieving ALT levels near the subject's baseline to limit hepatocellular toxicity and possibly ameliorate reduction of transgene expression over the period when ALT elevations have been observed.

At the highest dose tested in 270-201 (6E13 vg/kg), the majority of subjects achieved FVIII activity above 50 IU/dL at 52 weeks post-infusion. Subjects in that cohort 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.

In 270-301, an interim analysis has shown increased FVIII activity in the majority of subjects to mild HA or normal levels at 26 weeks post-infusion, also with markedly decreased bleeding compared with pre-study rates and the ability to discontinue prophylactic FVIII infusions. All subjects who will be included in the final analysis have been dosed with 6E13 vg/kg and continue to be followed.

The current data available has shown an established positive benefit:risk profile for BMN 270 at the 6E13 vg/kg dosing level, although the impact of prophylactic corticosteroids requires further investigation. 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 270-303 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LTs 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 the risks and benefits of treatment with BMN 270, refer to the current version of the Investigator's Brochure.

7.4.1 Optional Liver Biopsy Risks and Benefits

Liver biopsy is considered a safe procedure, with serious complications occurring less than once in every 10,000 procedures (Grant, 2004). Although the theoretical risks of significant complications are extremely small, the main complications would include bleeding and bile leakage. Another theoretical complication is infection at the needle insertion site; the sterile technique used makes this risk extremely small.

The most common problems include mild pain and a minor decrease in blood pressure. More serious complications, such as bleeding, infection, and injury to nearby organs, are very rare, but the subject will be monitored appropriately to ensure correct management should any of these occur. Any complications related to the liver biopsy should be reported as adverse

events, as outlined in Section 10. The liver biopsy is a standard investigation, and will be explained more fully by the experienced clinician performing the biopsy.

Each subject who participates in this optional sub-study will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. Timing of the liver biopsies will occur at Weeks 26, 52, and/or during Years 2-5. Safety will be assessed by adverse event reporting and clinical laboratory assessments. Per the Investigator's discretion and/or according to local guidelines, the subject may be kept in overnight following the liver biopsy for additional safety monitoring; such an overnight stay would not be considered a hospitalization for serious adverse event (SAE) reporting purposes (refer to Section 10.4.1.7).

There is no direct benefit from participating in this study other than contributing to understanding the mechanism of action of BMN 270. Consenting into this specific sub-study is optional and will not have any effect on the subject’s continued participation in 270-303.

8 STUDY OBJECTIVES

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to Week 52 for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to Week 52 for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

The safety objectives of the study are to:

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

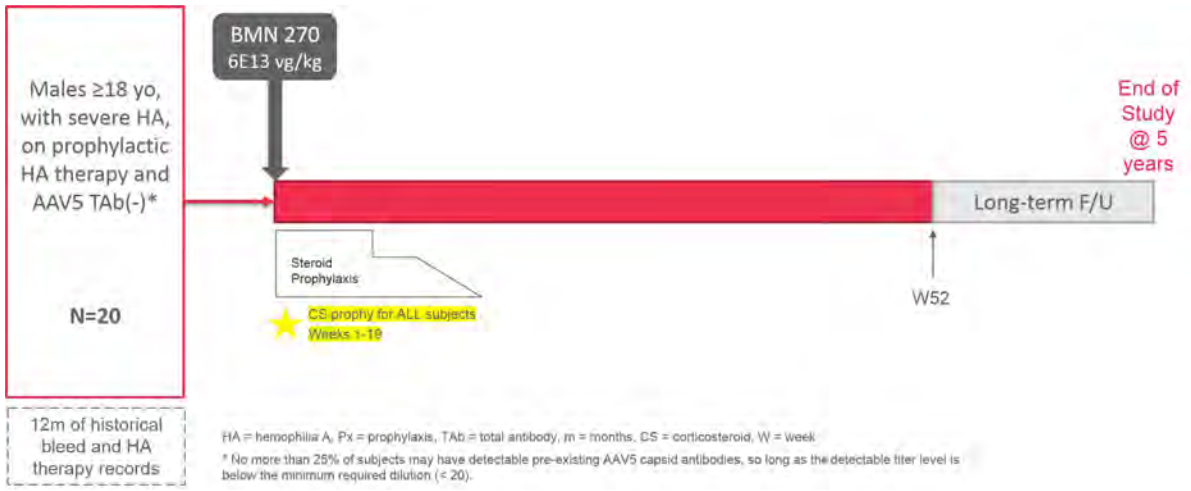
9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 10 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. Post-infusion, subjects will be eligible to receive on-demand corticosteroids, as indicated. (Figure 9.1.1).

Figure 9.1.1: 270-303 Study Schema



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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as either failure to achieve FVIII activity $\geq$ 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and consultation with the Investigator and the Medical Monitor. Therapeutic oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

Schedules of events 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 the optional liver biopsy (Table 9.1.5) 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)[n]
	Screening		Smart Rescreening[l] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[m]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Informed consent	X	X[o]			
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 hemophilia therapy usage for previous 12 months (by either subject or clinical information)		X	X	X	
Distribution of subject diaries and training in their use[b]		X			
Electrocardiogram		X			
Liver Ultrasound/FibroScan		X			
hFVIII Assays[c]		X	X[p]	X	
hFVIII TAb		X		X	
Screen for Hepatitis B, Hepatitis C, HIV[d]		X			
Screen for COVID-19 (local or central)[e]		X	X		
Blood chemistry, hematology, and coagulation tests[f]		X	X	X	
Fasting lipid panel (blood triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol)					X
Fasting FibroTest					X

Assessment	Prior to BMN 270 Infusion				BMN 270 Infusion Visit (Day 1)[n]
	Screening		Smart Rescreening[l] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[m]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Urine Tests[f]		X	X	X	
Liver Tests[f]		X	X	X	
AAV5 TAb Assay (CDx)[g]	X	X	X		X
Immunogenicity AAV5 TAb Assay				X	X
AAV5 TI Assay				X	X
IFNg ELISpot				X	
Plasma, PBMC, and RBC collection for exploratory biomarkers[h]				X	
Biomarker testing[h]		X			
Serum for exploratory biomarkers[i]		X			X
Exploratory CK18 and Grp78 assessment		X		X	
TGA Assay[i]				X	
Haemo-QoL-A assessment				X	
EQ-5D-5L				X	
WPAI+CIQ:HS				X	
PROBE				X	
PCR of vector DNA in blood, saliva, urine, semen, and stools				X	X
Pharmacokinetics				X[q]	
BMN 270 Infusion					X
Complement Panel[j]				X	X
Hypersensitivity blood assessments[k]					X

* 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] 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.

[c] Includes baseline FVIII activity (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), coagulation exploratory assay, chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, 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).

[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] COVID-19 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing.

[f] 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 at Screening.

[g] Screening, Smart Re-screening, and Infusion Day samples will be tested using the CDx AAV5 total antibody (TAb) assay. During Screening, the CDx AAV5 TAb assay test may be done first, under a standalone informed consent form, before the main ICF for the study is signed and further screening procedures are performed. If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening. Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.

[h] Includes HLA genotyping and FVIII genotyping.

[i] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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, as well as testing of the thrombin generation assay (TGA) sample, will be performed only as deemed necessary by the Sponsor.

[j] Complement panel should include C3, C3a, C4, Bb, and sC5b-9 (refer to Table 9.7.7.2.1) and should be collected 2 hours after completion of the infusion.

[k] In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory cytokine bead array (CBA) to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

[l] 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. COVID-19 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. 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.

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

[n] With the exception of the collection of samples for polymerase chain reaction (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 analysis (blood, saliva, urine, semen, stool) should be collected between 2 and 24 hours after the infusion has been completed.

[o] If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

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

[q] Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

Table 9.1.2: Schedule of Events-Post-Infusion Follow-Up (Week 1-20)

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	**2[f]**	**3[f]**	**4**	**5[f]**	**6[f]**	**7[f]**	**8**	**9[f]**	**10[f]**	**11[f]**	**12**	**13[f]**	**14[f]**	**15[f]**	**16**	**17[f]**	**18**	**19[f]**	**20**
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
Physical examination[a]				X				X				X				X		X		X
Weight				X				X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs				X				X				X				X				X
Blood chemistry, hematology, and coagulation tests[b]				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	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	X			X				X				X				X				X
Immunogenicity AAV5 TAb Assay				X				X								X				
AAV5 TI Assay				X				X								X				
hFVIII TAb				X				X				X				X				X
IFNg ELISpot		X				X				X				X				X		
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]	X			X				X				X						X		
Complement Panel[b]	X	X		X				X				X				X				X
Serum for exploratory biomarkers[e]	X	X		X		X		X		X		X				X				X
Exploratory CK18 and Grp78 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	**2[f]**	**3[f]**	**4**	**5[f]**	**6[f]**	**7[f]**	**8**	**9[f]**	**10[f]**	**11[f]**	**12**	**13[f]**	**14[f]**	**15[f]**	**16**	**17[f]**	**18**	**19[f]**	**20**
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
TGA Assay[c]																X				X
Haemo-QOL-A assessment				X								X								
EQ-5D-5L				X								X								
WPAI+CIQ:HS				X								X								
PROBE				X								X								
Testing for reactivation of hepatitis B and hepatitis C						X[g]														X[g]

[*] Visit windows are ± 48 hours.

[a] Brief physical examination should be done at scheduled visits. Additional physical exams may be done at the discretion of the PI.

[b] Refer to Table 9.7.8.2.1for laboratory assessments to be included and for complement panel tests, 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 > upper limit of normal (ULN) or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Collection and testing of semen samples must continue at least through Week 12, even if 3 consecutive results below the limit of detection in that compartment have already been recorded.

[e] Blood samples will be collected 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.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

Table 9.1.3: Schedule of Events – Post-Infusion Follow-Up (Weeks 21-52)

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	**22**	**23[f]**	**24**	**25[f]**	**26**	**28**	**30[f]**	**32**	**34[f]**	**36**	**40**	**44**	**48**	**50[f]**	**52**
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Physical examination[a]		X		X		X	X		X		X	X	X	X		X
Weight						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	X	X	X	X
Vital Signs				X		X			X		X	X	X	X		X
Blood chemistry, hematology, and coagulation tests[b]						X			X		X		X			X
Urine Tests[b]						X					X					X
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]						X			X		X		X			X
Immunogenicity AAV5 TAb Assay						X					X					X
AAV5 TI Assay						X					X					X
hFVIII TAb				X		X					X					X
IFNg ELISpot		X		X		X					X					X
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]		X				X	X				X		X			X
Complement Panel[b]				X		X					X					X
Serum for exploratory biomarkers[e]				X		X					X					X
Exploratory CK18 and Grp78 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TGA Assay[e]						X			X		X		X			X

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	22	23[f]	24	25[f]	26	28	30[f]	32	34[f]	36	40	44	48	50[f]	52
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Haemo-QOL-A assessment						X										X
EQ-5D-5L						X										X
WPAI+CIQ:HS						X										X
PROBE						X										X
Testing for reactivation of hepatitis B and hepatitis C									X[g]							
Optional liver biopsy[h]						X										X

[*] Visit windows are ± 48 hours.

[a] Brief physical examination should be done at all visits where a physical examination is indicated except Week 26 and Week 52, where a complete physical examination should be performed Additional physical exams may be done at the discretion of the PI.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included and for complement panel tests, 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 > ULN or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator.

[e] Blood samples will be collected 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.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

[h] Optional liver biopsy should be obtained within two weeks of Week 26. Additional follow-up liver biopsy will be obtained within two weeks of Week 52. Subjects should fast for at least 8 hours prior to liver ultrasound and optional liver biopsies.

Table 9.1.4: Schedule of Events-Post-Infusion Follow-Up (Year 2-Year 5)

Assessment	Years 2-5*			End of Year Visit				ETV
	Years 2-5	Year 2	Year 3-5	Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
Physical examination[b]	X			X				X
Weight[b]	X[a]			X[a]				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and hemophilia therapy use)	X	X	X	X				X
Vital Signs	X			X				X
Blood chemistry, hematology, and coagulation tests[c]	X[a]			X[c]				X
Urine Tests[c]	X[a]			X[c]				X
Liver Tests[c]	X	X	X	X				X
hFVIII assays[d]	X	X	X	X				X
PCR of vector DNA in blood, saliva, urine, and stools	(X)[e]			(X)[e]				(X)[e]
PCR of vector DNA in semen	(X)[e]	(X)[e]	(X)[e]	(X)[e]				(X)[e]
Immunogenicity AAV5 TAb Assay				X				X
AAV5 TI Assay				X				X
hFVIII TAb	X			X				X
IFNg ELISpot[a]	X[a]			X				X
Plasma, PBMC, and RBC collection for exploratory biomarkers[f]	X			X				X
Serum for exploratory biomarkers[f]	X			X				X
Exploratory CK18 and Grp78 assessment	X	X	X	X				X
TGA Assay[f]				X				X
Haemo-QoL-A assessment	X[a]			X[a]				X
EQ-5D-5L	X[a]			X[a]				X

Assessment	Years 2-5*			End of Year Visit				ETV
	Years 2-5	Year 2	Year 3-5	Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
WPAI+CIQ:HS	X[a]			X[a]				X
PROBE	X[a]			X[a]				X
Optional liver biopsy[h]				X				

* Visit windows are ± 2 weeks for visits in Years 2-5.

[a] These assessments need to be performed only at every other Q12W and every End of Year visit (ie, Weeks 76, 104, 128, 156, 180, 208, 232, and 260).

[b] 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.

[c] 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 > ULN or ≥ 1.5x 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value; (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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

[d] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay 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.

[e] Sample testing during Years 2-5 is not required if at least 3 consecutive samples were below the limit of detection during Year 1; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Subjects who have not had 3 consecutive semen samples below the limit of

detection 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 samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

[f] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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, as well as testing of the TGA assay sample, will be performed only as deemed necessary by the Sponsor.

[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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in semen 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. Unscheduled visits may also be conducted by MN as appropriate.

[h] An optional liver biopsy may be performed at any time between Years 2-5 of the study. The optional biopsy would be triggered by a FVIII activity decline by > 50% from steady-state, over 2 consecutive measurements, or by a sustained ALT rise > ULN. If neither trigger is observed, the optional biopsy should be performed at the end of Year 5.

Table 9.1.5: Schedule of Events-Optional Liver Biopsy

	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	Biopsy Day (BD)
Informed Consent for Liver Biopsy Procedure	X		
Liver Ultrasound[a]	X		
Physical examination	X		X
Hematology, Coagulation, Chemistry Assessments[b]	X		X
Liver Tests[b]	X		X
FibroScan	X		
FVIII Activity Level Assessment (central and local)		X	X[*]
Exploratory CK18 and Grp78 assessment		X	X[*]
Pre-Biopsy Consultation[c]		X	
Liver Biopsy[d]			X
PBMC Collection (whole blood draw)			X[e]

[*] If the Day -7 and biopsy day visits occur on the same day, these tests do not need to be duplicated.

[a] Liver ultrasound must be performed within 28 days prior to the scheduled biopsy. Subjects should fast for at least 8 hours prior to liver ultrasound.

[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.

[c] Subjects will undergo a pre-biopsy consultation with the Investigator (treating hematologist) and hepatologist and/or radiologist.

[d] Subjects should fast for at least 8 hours prior to optional liver biopsy. Biopsy will be a percutaneous or transjugular biopsy under ultrasound guidance, performed according to the standard procedure of the institution. If only a small amount of tissue (< 2 cm) is obtained at the time of the biopsy, the subject may be asked to consent for a second pass. In this case, the original < 2 cm sample should still be retained and handled according to the instructions for handling biopsy specimens in the Laboratory Manual. Following completion of the biopsy, the subject should remain in the hospital under observation for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion.

[e] Blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

Table 9.1.6: Suggested Schedule of Events-Prophylactic Corticosteroids

	Corticosteroid Treatment Period[b]																			Post-Corticosteroid Period[c]				
		Week																		Week				
Assessment	**D1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**32**
Prophylactic corticosteroid dose (mg/day)	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	35 mg	35 mg	30 mg	30 mg	25 mg	25 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis B testing[d]							X														X				X
HCV Viral Load[d]							X														X				X

[a] This table provides an example of a prophylactic corticosteroid course. Clinical judgment, weighing the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses, and discussions between the Investigator and Medical Monitor are advised for any questions or concerns. Dosages are for prednisone or an equivalent dose of another corticosteroid. FVIII and liver tests are also reflected in the Schedule of Events for the study.

[b] Following initiation or completion of corticosteroid regimen, if a recurrence of ALT values > ULN or ≥ 1.5x 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, relationship between increases in ALT and FVIII activity, ALT levels/FVIII activity post-corticosteroid initiation, and adverse events related to corticosteroid dosing. Guidance for tapering oral corticosteroid dosing can be found in Section 9.4.8.2, although a discussion between the PI and Medical Monitor should take place prior to tapering the corticosteroid dose.

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

[d] Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry. Tests are also reflected in the Schedule of Events for the study.

9.2 Discussion of Study Design

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

Given that BMN 270 is likely a one-time treatment, due to antibody formation against the AAV5 capsid post-infusion, and the well-characterized clinical experience of patients with severe hemophilia A on currently available chronic therapies, having a separate control group in this study was deemed to be inappropriate and unnecessary, as has been the case with all AAV gene therapy trials to date.

Approximately 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a prophylactic corticosteroid regimen. Post-infusion, subjects will be eligible to receive on-demand corticosteroids, as indicated.

9.3 Selection of Study Population

Approximately 20 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 hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
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 viral vector DNA below the limit of detection.
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. Up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the titer level is below the minimum required dilution (< 20).
2. Any evidence of active infection, including COVID-19, 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. FibroScan or 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 FibroScan or 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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.
16. 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 and/or use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.
19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.

20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

9.3.2.1 Optional Liver Biopsy Inclusion and Exclusion Criteria

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

1. Able to sign informed consent and comply with requirements for the optional liver biopsy
2. Documentation of FVIII activity ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII levels activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist/radiologist would make liver biopsy contraindicated. This includes (but is not limited to) abnormalities detected on liver ultrasound performed within 28 days of procedure, or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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.

Subjects may be considered lost to follow-up if the subject has missed 3 consecutive visits in the study and has failed to communicate a reason for this to the site. In addition, the site has documented at least 4 attempted contacts by key research personnel to reach the subject without success in the following manner:

- 2 attempts by telephone or email (if possible); then
- If telephone/email contacts are unsuccessful, 2 attempts must be made by certified letter or by appropriate local process.

Where communication has been made by phone, this should be documented in the subject source notes.

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. 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 electronic case report form (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, and 260 weeks of post-infusion 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

BMN 270 is a sterile, clear, colorless-to-pale yellow solution for IV infusion and is supplied in a 10 mL Crystal Zenith® (CZ) vial. Each vial contains 8.5 mL (extractable volume 8 mL) of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The IP 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 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.

BMN 270 will be prepared and infused as a pure solution over a dose-dependent time. Prepared drug will be kept at room temperature prior to administration. Refer to the Pharmacy Manual for IP administration instructions.

BMN 270 will be infused through the catheter using an appropriate infusion pump at an initial rate of 1 mL/min. The infusion rate should be increased every 30 minutes by 1 mL/min up to a maximum of 4 mL/min, provided that the subject's clinical condition permits such an increase. Of note, the IP has been shown to be stable at room temperature for 10 hours following completion of product thaw. 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 after an infusion-related reaction. At the restart, the infusion rate may be adjusted (ie, to a slower rate [minimum of 1 mL/min], with the rate increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min, if the subject's clinical condition permits such an increase) with careful monitoring of the subject. In the event of an infusion rate reaction with more than one dosing interruption, the infusion rate would not go beyond 1mL/min.

In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory cytokine bead array (CBA) to assess

inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor. Exploratory biomarker samples at baseline and at post-infusion study visits may also be used to assess changes in these biomarkers to better elucidate the mechanisms of infusion-related hypersensitivity reactions. Inpatient 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; inpatient observation can be extended beyond 8 hours if needed per Investigator discretion. After the observation period, subjects will be discharged from the clinic unless toxicity has been observed in which case the stay in the clinic may be extended 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 20 subjects will be enrolled into the single arm study of 6E13 vg/kg with prophylactic corticosteroids. Up to 25% of the total number of patients dosed should have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening.

9.4.6 Selection of Dose Used in the Study

Data from previous human studies (270-201, 270-301) indicated that dosing at 6E13 vg/kg showed improvement in FVIII activity, bleeding episodes, and exogenous FVIII utilization and infusion rate. Dosing was well tolerated, with mild increases in ALT as the most common adverse event. Please refer to the IB for detailed efficacy and safety data.

This dose is expected to be safe and effective based on clinical experience to date in 270-201 and 270-301, as well as non-clinical data.

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 as needed (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
- Fitusiran
- Concizumab
- Efavirenz

The following medications and agents 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, including isotretinoin and dextroamphetamine/amphetamine
- Medications which may reduce or increase the plasma concentration of corticosteroids

Subjects should be counseled to avoid starting potentially hepatotoxic therapies and to inform the Investigator of any new medications prescribed by other physicians. Investigators should carefully consider both the mechanism of action and potential hepatotoxicity of any new medication prior to initiation. If a potentially concerning new medication is started, Investigators should closely monitor both FVIII activity and ALT levels (eg, weekly to every 2 weeks for the first month) in order to determine if any detrimental effects on the efficacy or safety of BMN 270 have occurred. If co-medications are required during the course of the study, where possible, please check the National Center for Biotechnology Information LiverTox website for potential hepatotoxicity issues prior to prescribing (NCBI, 2020).

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
- Non-steroidal anti-inflammatory drugs (NSAIDs)

9.4.8.1 Concomitant Hemophilia Treatments

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

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 Investigator 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 Corticosteroid Treatment and/or Alternative Immunosuppressive Agent Treatment of Elevated Hepatic Transaminases

Prior to dosing, all subjects must be screened per steroid prescription guidelines to ensure the subject is eligible to receive corticosteroid treatment as outlined in the protocol. Refer to corticosteroid prescription guidelines for recommended monitoring for, and management of, potential side effects of corticosteroids, including guidance on medications that should be avoided during corticosteroid treatment.

All subjects will be started on prophylactic corticosteroids starting on the day of infusion (Day 1). The first dose of prophylactic corticosteroids (40 mg of prednisone or prednisolone, or an equivalent dose of another corticosteroid) should be taken at least 3 hours prior to the start of the BMN 270 infusion and continued on a daily basis. Table 9.1.6 provides an example of a possible prophylactic corticosteroid course, including taper and post-corticosteroid additional monitoring of FVIII activity, LTs, and hepatitis B/hepatitis C reactivation. Clinical judgment, weighting the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses. Discussions between the Investigator and Medical Monitor are advised for any questions or concerns.

Following initiation or completion of the prophylactic corticosteroid regimen, if ALT levels become increased (eg, ≥ 1.5x baseline value or > ULN) and alternative etiologies have been ruled out, prompt institution of newly administered or an increased dose of therapeutic or on-demand oral corticosteroids (prednisone or an equivalent dose of another corticosteroid) should be considered after consultation with the Medical Monitor (refer to Table 9.7.8.3.2).

- Whenever possible, a confirmatory lab draw for ALT should be performed within 72 hours, along with FVIII activity, prior to initiating oral corticosteroids.
- Newly administered corticosteroids or dose increases are not indicated if elevations in ALT are clearly not related to BMN 270 (eg, elevated ALT with concurrent increase in CPK due to intensive exercise) although this should be discussed with the Medical Monitor.

- Alternative immunosuppressive agents may also be considered for use on a case-by-case basis and following consultation with the Medical Monitor (eg, if prolonged corticosteroid use is contraindicated).

Unless otherwise indicated, therapeutic corticosteroid treatment should be initiated at a dose of 60 mg/day. If the ALT level immediately returns to ≤ 1.5x baseline and FVIII activity levels continue to rise and/or remain within or above the normal range in the 2 weeks following corticosteroid initiation, on-demand corticosteroids can be discontinued. However, if this is not the case, therapeutic corticosteroids should be tapered over a longer period of time. At minimum, the recommended duration of on-demand corticosteroids is 60 mg/day for 3 weeks, 40 mg/day for 4 weeks, and 30 mg/day for 4 weeks, followed by a gradual taper thereafter. Should a scenario arise in which a deviation from the minimum recommended dose and/or duration of therapeutic corticosteroids may be clinically indicated, a discussion should take place between the Investigator and Medical Monitor regarding corticosteroid dose adjustments. Tapering of corticosteroid dosages should be guided by the following (Table 9.7.8.2.1):

Table 9.4.8.2.1: Adjustments to Corticosteroid Regimen

Corticosteroids should be tapered on an individual subject basis with the following guiding principles:	Corticosteroids may be tapered **if**: • ALT ≤ 1.5x baseline value; and • FVIII activity levels > 90% of the pre-decline FVIII activity levels; and • There is no concern for adrenal insufficiency post-withdrawal
Increasing Corticosteroid Dose	If ALT level is increasing or FVIII activity 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 on-demand 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 increased ALT levels (eg, > ULN or ≥ 1.5x baseline value) are 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 SoA. 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). Alternative, non-steroidal systemic immunosuppressive agents may be used, following a discussion between the Investigator and the Medical Monitor, should corticosteroid use be deemed by an Investigator to be clinically ineffective, not tolerated, and/or contraindicated. Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of oral corticosteroid/immunosuppressive agent treatment and then 1 week and 13 weeks after the completion of oral corticosteroid/immunosuppressive agent 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/immunosuppressive agent use) should be reported as outlined in Section 10 of the protocol.

Subjects on corticosteroids should receive appropriate counseling and support regarding side effects from the Investigator or the treating institution (eg, listings of side effects and when to notify carers, wallet card for emergencies if on steroids, etc.). Additional management, including the co-prescription of additional medications to prevent complications related to corticosteroid therapy, may be undertaken at the discretion of the investigator, including, but not limited to, prophylaxis against the occurrence of gastric ulcers, osteoporosis, and infections. The above guidance should also be followed in the event that an alternative immunosuppressive agent is used, as applicable.

9.4.9 Treatment Compliance

IP 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 IP containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP 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 standard operating procedures (SOPs).

9.5.1 Return and Disposition of Clinical Supplies

Unused IP 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 IP or study materials (or must be referenced in their institution SOPs).

Unused IP may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The study monitor must account for all IP in a formal reconciliation process prior to IP destruction. All IP 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 IP appropriately, the site can return unused IP to BioMarin upon request. The return of IP or IP materials must be accounted for on a IP return form provided by BioMarin.

All IP 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 starting at the time of informed consent for study participation and for the first 52 weeks of the study, and particularly within 48 hours prior to lab work. Alcohol use should be minimized throughout the remaining duration of the study.

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 blood and semen samples, respectively. Subjects should also abstain from organ donation.

9.7 Safety and Efficacy Variables

9.7.1 Safety and Efficacy Measurements Assessed

The Schedule of Events (Table 9.1.1 through Table 9.1.4) 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.

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 the end of 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.

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 include:

- Change in the annualized utilization (IU/kg/year) and infusion (number/year) rates of exogenous FVIII replacement therapy during Week 5 to Week 52 post-BMN 270 infusion from the baseline number and utilization of exogenous FVIII replacement therapy, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change in administration of exogenous FVIII replacement therapy Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis.
- Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) during Week 5 to Week 52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis, from the baseline ABR during the 12 months prior to study entry.

Subjects must have high quality documented historical data available concerning previous bleeding episodes and hemophilia treatment 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 or use of emicizumab.

9.7.3.2 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).

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.

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).

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).

Details (including sample copies where applicable) for each of the PRO instruments are provided in the Investigator Site File Binder.

9.7.4 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 chromogenic 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.

9.7.5 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.

9.7.6 Pharmacokinetics

Sparse FVIII activity assessments, prior to BMN 270 administration, will be collected to estimate each subject's half-life of replacement FVIII concentrate used for prophylaxis. Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. If supported by the data, sparse samples together with established population pharmacokinetic models will be used to estimate an individual subject's FVIII activity clearance (CL) value. Individual subject CL estimates may then be evaluated against post-BMN 270 FVIII activity levels to determine if an association exists between an individual's FVIII activity CL value and FVIII activity levels achieved with BMN 270. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

9.7.7 Exploratory Assessments

Blood samples will be collected from subjects at the time points indicated in the Schedules of Events 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.

9.7.7.1 Optional Liver Biopsy

Subjects electing to undergo an optional liver biopsy are required to consent to the procedure and collection of tissue in the study ICF. The analysis of the optional liver biopsy is considered exploratory. Patients who elect to proceed will have a liver biopsy performed around Week 26, Week 52, and/or during Years 2-5. Additional liver biopsies at times deemed to be clinically relevant (eg, decreasing FVIII at a time of increased ALT) may be pursued. Subjects will be asked to consent to the procedure for each liver biopsy performed during the study.

Subjects who consent to the procedure will have a liver biopsy via either transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. Two tissue cores will be harvested in the context of the optional liver biopsy. Subjects will be required to observe an 8-hour fasting period before the procedure.

Within 24 hours prior to the biopsy being performed, subjects must have a documented FVIII activity level of ≥ 50 IU/dL (or higher, depending on local guidelines and/or investigator discretion). FVIII activity levels for this purpose should be assessed at the local laboratory within 7 days before the biopsy and again on the day the biopsy, prior to the procedure. As needed, subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity levels to an appropriate level, under the supervision/instruction of the investigator, to ensure the safety of the subject during the procedure. This exogenous FVIII usage (if performed) should be recorded in the eCRF FVIII infusion pages under the category “Surgery/Procedure”.

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5 Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests
- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- Local FVIII activity level assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion and/or according to local guidelines.

Clinically significant findings reported from the histopathological analysis of the biopsy sample are subject to AE reporting (Section 10). Such findings should be further assessed and followed as clinically appropriate to manage the subject's medical care. A hepatologist and/or other specialist clinicians should be consulted if required. In the event that fibrotic changes are observed on the biopsy sample, additional liver ultrasound, FibroScan and/or Enhanced Liver Fibrosis (ELF) testing (as regionally available and/or approved by HA) may be considered at the discretion of the investigator and/or hepatologist.

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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

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.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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	**Complement Panel**
CPK	Differential cell count	Protein	C3
Creatinine	RBC indices (MCV and MCH)	Glucose	C3a
CRP		Bilirubin	C4
Glucose		Nitrite	Bb
Phosphorus		Urobilinogen	sC5b-9
Potassium		Hemoglobin	
Total protein			**Other Tests:**
Sodium			ABO blood typing*
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 at Screening.

In addition to scheduled clinical laboratory assessments, a fasting blood lipid panel (including triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) and FibroTest 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for an optional, exploratory CBA to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

At applicable sites, certain study assessments may be performed by an 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 at the visits indicated in the Schedules of Events. Unscheduled visits may also be conducted by MN as appropriate.

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 negative surface antigen or DNA for hepatitis B or negative 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 the timepoints listed in Table 9.1.6. 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.

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

Where a biopsy has been taken for safety-related reasons or was available from a past procedure, the Sponsor may request the biopsy information to help evaluate the impact of BMN 270 on the liver. The Sponsor may request that slides from a liver biopsy be made available for additional histopathological review.

LTs 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 (note that these evaluations may indicate additional testing of LTs and FVIII levels at unscheduled visits; these unscheduled laboratory tests may be completed by a mobile nursing professional at sites where the use of MN services has been approved):

Table 9.7.8.3.2: Evaluation of ALT Elevations

ALT Level	Work-Up
≥1.5x Baseline - <2x Baseline	• Continue to monitor LTs and FVIII per protocol (repeat within 24-72 hours if next protocol scheduled visit is >24-72 hours 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 or > 2x baseline in 2 consecutive assessments within 24-72 hours and alternative etiologies have been ruled out, start oral corticosteroids upon consultation with the Medical Monitor (refer to Section 9.4.8.2) • Consider liver biopsy at the discretion of the Investigator or Medical Monitor
≥2x Baseline or > ULN - <3x ULN	• Repeat LTs and FVIII within 24-72 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 ≥ 2x baseline or > ULN - < 3x ULN 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) • 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
≥3x ULN	• Consult with Medical Monitor • Evaluate and rule out alternative etiologies (as above) • Repeat LTs and FVIII within 24-48 hours, and continue with monitoring of LTs at least twice weekly for as long as the subject's ALT remains ≥ 3x ULN

ALT Level	Work-Up
	• In the event that ALT or AST is ≥3x ULN and total bilirubin is ≥2x ULN, albumin and PT/INR should also be obtained. • 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 the timepoints indicated in the schedules of events. 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 should be performed during Screening/Baseline, at Week 26 (± 2 weeks) 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.

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 at the timepoints indicated in the Schedules of Events.

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. Testing will continue until at least 3 consecutive results below the limit of detection are obtained; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. If a positive result is obtained in a matrix after 3 consecutive results below the limit of detection have already been recorded, testing in that matrix should restart and continue until an additional 3 consecutive results below the limit of detection have been obtained in order to confirm clearance.

Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point. Subjects who have not had 3 consecutive semen samples below the limit of detection by Week 52 should continue to have PCR testing in semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

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, stool). 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, after consultation between the Medical Monitor and the Investigator, 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 below the limit of detection for vector DNA on at least three consecutive visits.

Contraception use may need to be extended beyond 12 weeks in individual subjects based on observed vector shedding in semen. After 12 weeks, subjects may stop contraception use only if they have had 3 consecutive semen samples below the limit of detection (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.

  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 > ULN or ≥ 1.5x baseline value, regardless of whether that elevation triggers an initiation or modification of oral corticosteroid treatment
- Events potentially meeting the criteria for Hy's law (ALT or AST elevation ≥ 3x ULN plus total bilirubin ≥ 2x ULN)
- Thromboembolic event
- Immediate reactions: infusion-related reactions, hypersensitivity adverse events, or anaphylaxis
- 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/or concomitantly administered corticosteroids and/or other immunosuppressive agents, 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 Common Terminology Criteria for Adverse Events (NCI CTCAE) v5. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5as 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/or corticosteroids and/or other immunosuppressant agents 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 and/or corticosteroids and/or other immunosuppressive agents has not occurred **OR** • The administration of the IP and/or corticosteroids and/or other immunosuppressive agents 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 and/or corticosteroids and/or other immunosuppressive agents; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP and/or corticosteroids and/or other immunosuppressive agents.
Related	• The administration of the IP and/or corticosteroids and/or other immunosuppressive agents and the occurrence of the AE are reasonably related in time **AND** • The AE could not possibly be explained by factors or causes other than exposure to the IP and/or corticosteroids and/or other immunosuppressive agents **OR**
	• The administration of IP and/or corticosteroids and/or other immunosuppressive agents and the occurrence of the AE are reasonably related in time **AND** • The AE is more likely explained by exposure to the IP and/or corticosteroids and/or other immunosuppressive agents 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 and/or corticosteroid and/or other immunosuppressive agent exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug and/or corticosteroid and/or other immunosuppressive agent action
- Similarity to adverse reactions seen with related drug products

- Abatement of AE with discontinuation of study drug and/or corticosteroids and/or other immunosuppressive agents, and/or recurrence of AE with reintroduction of study drug and/or corticosteroids and/or other immunosuppressive agents

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 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.

10.4.1.3 Abnormal Laboratory Values

Laboratory test results (including any local FVIII activity or liver 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 unless associated with an AE that has already been reported.

Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF, unless the abnormal laboratory results has been reported or captured as part of an AE that has already been reported.

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).

10.4.1.4 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).

10.4.1.5 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.

10.4.1.6 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

10.4.1.7 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.

10.4.1.8 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 BioMarin Pharmacovigilance (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 electronic data capture (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 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: PI
Fax: PI
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: PI, MD, MHS
Address: 105 Digital Drive
Novato, CA 94949 USA
Phone: PI
E-mail: PI

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.

During the first part of the Screening Period (Day -42 to Day -29), testing for AAV5 TAb titers using the CDx screening assay may be performed, so that subjects can verify their AAV5 TAb status. Subjects who agree to participate in this activity may be asked to sign a separate ICF documenting this decision. Subjects who do not have testing during this period will have CDx AAV5 TAb testing along with the rest of the Screening assessments.

If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

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 hemophilia 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 Investigator Site File Binder.
- Distribution of subject diaries and training in diary completion
- Electrocardiogram
- Liver ultrasound/FibroScan
- 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)
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - hFVIII protein assay (collected but not tested prior to enrollment)
- hFVIII total antibody (TAb) assay (collected but not tested prior to enrollment)
- 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.
- Screen for COVID-19 (local or central testing)
    - COVID-19 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing.
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
    - ABO blood typing assessment should be performed at Screening
- Urine tests (refer to Table 9.7.8.2.1)
- Liver tests (refer to Table 9.7.8.3.1)
- AAV5 TAb Assessment (CDx)
    - If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening
- Biomarker testing (including HLA genotyping and FVIII genotyping status)

- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment

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))
- 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)
- Screen for COVID-19 (local or central testing)
    - COVID-19 RT-PCR testing is required during smart rescreening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing.
- AAV5 TAb Assessment (CDx)

12.3 Baseline Visit

Baseline values will be recorded from 1 to 7 days prior to the treatment visit. Subjects are considered enrolled into the study once the Baseline visit has occurred. 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)
- 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - hFVIII protein assay
- hFVIII TAb
- 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)
- Immunogenicity AAV5 TAb assay
- AAV5 TI assay
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Complement Panel
- Exploratory CK18 and Grp78 assessment
- TGA Assay
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Pharmacokinetics
    - Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

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:

- Initiation of prophylactic corticosteroids (at least 3 hours prior to BMN 270 infusion)
- Brief physical examination
- 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.
- Assessment of adverse events and concomitant medications
- 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.
- Fasting FibroTest
- AAV5 TAb Assay (CDx) (sample collected pre-infusion for analysis)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- Serum for exploratory biomarkers
- BMN 270 Infusion
- Complement panel (should be collected 2 hours after completion of the infusion)
- Hypersensitivity blood assessments (if required, see below)
- 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible,

1 week after the event for an optional, exploratory CBA to assess inflammatory biomarkers and plasma cytokine levels. Inpatient 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 have weekly assessments during Weeks 1-26. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At the Week 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:

- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- Exploratory CK18 and Grp78 assessment

12.5.2 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
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Complement Panel

12.5.3 Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 26

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

- Serum for exploratory biomarkers

12.5.4 Weeks 2, 4, 8, 12, 16, 20, 24, and 26

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

- Complement Panel

12.5.5 Weeks 2, 6, 10, 14, 18, 22, 24, and 26

At Weeks 2, 6, 10, 14, 18, 22, 24, and 26, the following procedure will be performed:

- IFNg ELISpot

12.5.6 Weeks 4, 8, 12, 16, 20, 24, and 26

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

- Vital Signs
- Weight (not done at Week 24)
- hFVIII TAb
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not done at Week 24)
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained. Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point.

12.5.7 Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26

At Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26, the following procedures will be performed:

- Brief physical examination

- A complete physical examination should be done at Week 26.

12.5.8 Weeks 4, 8, 16, and 26

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

- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay

12.5.9 Weeks 4, 8, 12, 18, 22, and 26

At Weeks 4, 8, 12, 18, 22, and 26, the following procedure will be performed:

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.5.10Week 4, 12, and 26

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

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

12.5.11 Weeks 4, 16, and 26

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

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

12.5.12 Weeks 12 and 26

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

- Urine Tests (refer to Table 9.7.8.3.1)

12.5.13 Weeks 16, 20, and 26

At Weeks 16, 20, and 26, the following procedure will be performed:

- TGA Assay

12.5.14 Weeks 6 and 20

At Weeks 6 and 20, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

12.5.15 Week 26

At Week 26 (± 2 weeks), the following optional procedure will be performed:

- Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)

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

After Week 27, subjects will have assessments at Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At these visits, the following assessments will be performed.

12.6.1 Each Visit (Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52)

The following procedures will be performed at every visit (Week 26, 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52):

- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- Exploratory CK18 and Grp78 assessment

12.6.2 Weeks 28, 32, 36, 40, 44, 48, and 52

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

- Brief physical examination (complete physical examination at Week 52)

12.6.3 Week 28, 36, 44, and 52

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

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.6.4 Week 32

At Week 32, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

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

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

- Vital Signs

12.6.6 Weeks 32, 36, 44, and 52

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

- Weight
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained.
- TGA assay

12.6.7 Week 36 and 52

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

- Urine Tests (refer to Table 9.7.8.3.1)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- hFVIII TAb

- IFNg ELISpot
- Complement Panel
- Serum for exploratory biomarkers

12.6.8 Week 52

At Week 52, the following procedure will be performed:

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

12.6.9 Week 52

At Week 52 (± 2 weeks), the following optional procedure will be performed:

- Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)

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 and Q6W visits during Years 2-5; 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. Unscheduled visits may also be conducted by MN as appropriate.

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 semen 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. Subjects who are not

attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

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

12.7.1 Year 2 (Every 4 Weeks) or Years 3-5 (Every 6 Weeks) (not required for treatment failure subjects)

During Years 2 (every 4 weeks ±2 weeks) or 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
        - If a subject tests positive in the cNBA 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
- Exploratory CK18 and Grp78 assessment
- PCR of vector DNA in semen (if required)
    - Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear by the end of Year 1. Subjects who have not had 3 consecutive semen samples below the limit of detection by the end of Year 1 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 samples below the limit of detection 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 semen must still provide semen samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

12.7.2 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 (final study visit)

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.

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)
- Vital Signs
- 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)
- 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 > ULN or ≥ 1.5x 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
        - If a subject tests positive in the cNBA 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
- Immunogenicity AAV5 TAb Assay (at End of Year visits only)
- AAV5 TI Assay (at End of Year visits only)
- hFVIII TAb
- Interferon gamma (IFNg) ELISpot (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment
- TGA Assay (at End of Year visits only)
- 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)
- 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)
- 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 below the limit of detection during the Post-Infusion Follow-Up period in Weeks 1-52.
- Optional liver biopsy (Years 2-5) (refer to Section 12.9 for assessments related to liver biopsy)

12.8 Early Termination 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 ETV. The Early Termination Visit (ETV) will occur on the date the subject withdraws from the study, even if the date does not correspond to a protocol-specific visit. At the ETV, as many of the following assessments as possible should be done:

- Complete 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - FVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- hFVIII TAb
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment
- TGA Assay
- Haemo-QoL-A assessment
- EQ-5D-5L

- WPAI+CIQ:HS
- PROBE

12.9 Optional Liver Biopsy

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5. Subjects may be asked to provide a liver biopsy around Week 26, Week 52, and during the Years 2-5 period post-BMN 270 infusion.

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- FVIII activity level assessment (central and local)
- Exploratory CK18 and Grp78 assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the investigator's discretion and/or according to local guidelines.

12.10 End of Study

The study will end after the last subject yet to complete the Week 260 visit 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.

Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

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 analyses. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

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.

Missing data imputation and sensitivity analyses to assess the impact of missing data on the primary and secondary efficacy endpoints analyses are described in the following sections. 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 at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels ≤ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose hFVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 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 14.9.

14.3 Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion:

- Change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy during Weeks 5-52 post-BMN 270 infusion, for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab during Week 27 to Week 52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis
- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment during Weeks 5-52 post-BMN 270 infusion for subjects receiving prior FVIII prophylaxis, or Weeks 27-52 post-BMN 270 infusion for subjects receiving prior emicizumab prophylaxis

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

The missing value of the change for annualized utilization and annualized infusion rate will be imputed as 0. The missing value of the change for annualized number of bleeding episodes will be imputed using the median value of the changes of all observed cases.

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, repeated within subject. The actual

number of bleeding episodes will be used as the dependent variable with the time period adjustment (annualization) 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.

14.4 Tertiary Efficacy Endpoints

The analyses of the tertiary efficacy endpoints will be descriptive. Mean change from baseline and associated 95% confidence interval will be provided for EQ-5D-5L, WPAI+CIQ: HS and PROBE scores at Week 52 post-BMN 270 infusion.

14.5 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.

14.6 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).

14.7 Safety Analysis

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

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.

14.8 Determination of Sample Size

Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects who have an AAV5 antibody titer that is detectable but below the minimum required dilution at Screening. For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that

the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

14.9 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

Subjects with an AAV5 antibody titer detectable but below the minimum required dilution will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post BMN 270 infusion.

14.10 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 must be sought, and the Investigator should inform BioMarin and the full IRB/IEC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC 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 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, 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 continue enrolling subjects based on emerging data and the overall risk/benefit analysis of BMN 270.
- Making other recommendations on the conduct and reporting of the trial based on their evaluation of clinical data.

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 SAP.

16 COSTS, COMPENSATION, AND SUBJECT INJURY

BioMarin will pay the full costs of the study-related tests, procedures, and treatments set forth in the protocol. In addition, after IRB/IEC approval, BioMarin may reimburse the reasonable cost of travel for study-related visits in accordance with BioMarin's travel and reimbursement policy.

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. 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. If this is the case, BioMarin will comply with the law. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort related solely to the study subject's primary disease or any concurrent disease that are unrelated to this study.

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 date and 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. 1995;19:1409-1417.

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

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. 2012;18(Suppl.6):1-13.

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.

Grant A, Neuberger J, Day C, Saxseena S. British Society of Gastroenterology Guidelines on the use of Liver Biopsy in Clinical Practice. 2004. Available at: https://www.bsg.org.uk/resource/bsg-guidelines-on-the-use-of-liver-biopsy-in-clinical-practice.html (last visited 20 January 2020).

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

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

Iorio A, Stonebraker JS, Chambost H, et al, for the Data and Demographics Committee of the World Federation of Hemophilia. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-546.

Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia 1. Blood. 2013;122(22):3568-3574.

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.

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. 2014;371(21):1994-2004.

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.

National Center for Biotechnology Information (NCBI). LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Available at: https://livertox.nih.gov (last accessed 20 August 2020).

National Hemophilia Foundation. MASAC recommendation for liver biopsies in gene therapy trials for hemophilia. 2019. Available at https://www.hemophilia.org/sites/default/files/document/files/256.pdf (last accessed 20 August 2020).

Pasi KJ, Rangarajan S, Mitchell N, Lester W et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med. 2020;382(1):29-40.

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.

Reilly M. WPAI Scoring. 2002. Available at: http://www.reillyassociates.net/WPAI_Scoring.html (last accessed 4 September 2020).

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. 2013;19(1):e1-47.

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

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 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. Additionally, he or she will not make any changes in the research without IRB/EC 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 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

Protocol Number: 270-303 Amendment 1

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:

DocuSigned by:
PI
Signer Name: PI
Signing Reason: I have reviewed this document
Signing Time: PI
88C2AD8975734CD9903DCA30AEEA33E4

Medical Monitor Signature Date

Printed name: PI MD, MHS, PI Clinical Sciences

24 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):

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

   b. 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 original protocol and relates the changes to the appropriate rationale (refer to pages 2-4). Added text is indicated by underlined font and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	Revision	Rationale
2/Synopsis (Study Design and Plan)	Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.	5
2/Synopsis (Exclusion Criteria)	Patients are excluded from the study if any of the following criteria apply: 2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, including HIV infection. 16. 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 corticosteroid treatment and/or the use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy results	1, 15
7.4/Summary of Overall Risks and Benefits	~~BMN 270 has an acceptable safety and tolerability profile that supports a positive benefit-risk assessment.~~Overall, 151 subjects have received a BMN 270 infusion at one of 4 dose levels (6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, or 6E13 vg/kg) in one of the four ongoing BMN 270 clinical studies (270-201, 270-301, 270-302, 270-203). Single infusions have been generally well tolerated by treated subjects across all investigated doses. All subjects have successfully completed their full-dose infusion of BMN 270, with no infusions requiring permanent termination prior to completion due to AEs. No deaths have been reported in any of the BMN 270 studies, and no participants discontinued from studies as a result of an AE. Frequency of adverse events decreased over time with no delayed adverse drug reactions. ~~Infusion~~Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) has been observed in most subjects administered BMN 270 shortly after dosing, with no symptoms or sequelae suggestive of clinically significant hepatocyte injury or liver dysfunction; no events meeting the Hy's Law criteria have been identified. ALT elevations have been reported as events of interest in 13 subjects in 270-201, 1 subject in 270-302, and 91 subjects in 270-301. Although the majority of events have been Grade 1 or Grade 2 in severity, 11 subjects (1 in 270-302 and 10 in 270-301) had a reported Grade 3 ALT elevation. Only one serious event of ALT increased has been reported by investigators (in addition to one event that BioMarin conservatively assessed as serious based on the details of the case). While the majority of ALT elevations responded rapidly to corticosteroids, given current interest in the field of AAV gene therapy for the use of non-steroidal approaches to managing or preventing ALT elevations, alternate non-steroidal systemic immunosuppressive agents have also been used to manage hepatic reactions where corticosteroids have proven to be ineffective or where high doses/and or prolonged exposure to corticosteroids have led to unwanted side effects. Overall, the literature and clinical experience with BMN 270 suggests that transient elevations in liver enzymes are expected following AAV-based gene	13

Section No./Title	Revision	Rationale
	therapy for the treatment for hemophilia A or B without any long-term concerns of hepatic injury (Manno, 2006; Nathwani, 2011; George, 2016; Miesbach, 2016; Pasi, 2017). Short-lived infusion reactions associated with one-time BMN 270 administration have included symptoms such as nausea, maculopapular rash, urticaria, ~~nausea,~~ diarrhea, watery eyes, rigors, chills, myalgia, fever, tachycardia and hypotension emerging within 24 hours of receiving BMN 270. ~~All of these events subsided without clinical sequela~~Most infusion-related reactions were Grade 1 or Grade 2 in severity, and all events resolved, typically within 48 hours following medical management. Three of these cases required temporary interruption of the infusion, followed by re-initiation at a slower rate. All subjects completed their infusions. The reactions with onset during or within approximately 5 hours after the end of infusion responded to treatment with systemic antihistamines and/or corticosteroids, where administered. Infusion-related reactions were effectively mitigated by managing infusion rate and medications. ~~Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) was observed in most subjects administered BMN 270 shortly after dosing, with no symptoms or sequelae suggestive of clinically significant hepatocyte injury or liver dysfunction. In almost all subjects, ALT elevations decreased quickly following corticosteroid treatment. There were differences in the use of corticosteroids across studies. Subjects in 270-201 received corticosteroids an average of 8 weeks earlier following BMN 270 infusion than the mITT population in 270-301, were more likely to avoid a significant decline in FVIII activity concurrently with an ALT elevation, and saw a more robust recovery of FVIII activity upon the first use of corticosteroids, than did the subjects in the mITT population in 270-301. Despite the clinical response to steroids, no associations between safety parameters (transient ALT rises), or efficacy as measured by FVIII activity levels were found to be temporally associated with anti-AAV5 antibody or cellular immune responses.~~ No subjects have experienced thromboembolic events or developed inhibitors to FVIII following BMN 270 infusion.	
9.1/Overall Study Design and Plan	Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.	5
Table 9.1.1	Table 9.1.1 has been updated to reflect changes made in the notes and elsewhere in the protocol.	1, 12, 15
Table 9.1.1 (notes)	[e] COVID-19 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. [j] Complement panel should include C3, C3a, C4, Bb, and sC5b-9 (refer to Table 9.7.7.2.1) and should be collected 2 hours after completion of the infusion. [l] 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. COVID-19 RT-	1, 12

Section No./Title	Revision	Rationale
	PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. 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.	
Table 9.1.2 (notes)	[b] Refer to Table 9.7.8.2.1for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.3.1 for liver tests (LTs).	15
Table 9.1.3 (notes)	[a] Brief physical examination should be done at all visits~~. Weight~~ where a physical examination is indicated except Week 26 and Week 52, where a complete physical examination should be ~~recorded~~performed Additional physical exams may be done at ~~all visits~~the discretion of the PI. [b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.3.1 for liver tests (LTs). [h] Optional liver biopsy should be obtained within two weeks of Week 26. Additional follow-up liver biopsy will be obtained ~~at~~within two weeks of Week 52. Subjects should fast for at least 8 hours prior to liver ultrasound and optional liver biopsies.	15
Table 9.1.4	Table 9.1.4 has been updated to reflect changes made elsewhere in the protocol.	14
Table 9.1.4 (notes)	[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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in semen 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. Unscheduled visits may also be conducted by MN as appropriate.	5
9.2/Discussion of Study Design,	Given that BMN 270 is likely a one-time treatment, due to antibody formation against the AAV5 capsid post-infusion, and the well-characterized clinical experience of patients with severe hemophilia A on currently available chronic	9

Section No./Title	Revision	Rationale
~~Including Choice of Control Group~~	therapies, having a separate control group in this study was deemed to be inappropriate and unnecessary, as has been the case with all AAV gene therapy trials to date.	
9.3.2/Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, including HIV infection. 16. 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 and/or use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.	1, 15
9.3.3/Removal of Subjects from Treatment or Assessment	Subjects may be considered lost to follow-up if the subject has missed 3 consecutive visits in the study and has failed to communicate a reason for this to the site. In addition, the site has documented at least 4 attempted contacts by key research personnel to reach the subject without success in the following manner: • 2 attempts by telephone or email (if possible); then • If telephone/email contacts are unsuccessful, 2 attempts must be made by certified letter or by appropriate local process. Where communication has been made by phone, this should be documented in the subject source notes.	10
9.4.8/Prior and Concomitant Medications	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: • ~~Lamivudine~~	7
Table 9.7.8.2.1/ Clinical Laboratory Tests	The specifics of the complement panel have been added to this table.	15
9.7.8.3/Liver and Hepatitis Testing	Where a biopsy has been taken for safety-related reasons or was available from a past procedure, the Sponsor may request the biopsy information to help evaluate the impact of BMN 270 on the liver. The Sponsor may request that slides from a liver biopsy be made available for additional histopathological review. ... Elevated ALT levels (above the upper limit of normal range) should be evaluated according to the following plan~~:~~ (note that these evaluations may indicate additional testing of LTs and FVIII levels at unscheduled visits; these unscheduled laboratory tests may be completed by a mobile nursing professional at sites where the use of MN services has been approved):	3, 8

Section No./Title	Revision	Rationale
Table 9.7.8.3.2/ Evaluation of ALT Elevations	• In the event that ALT or AST is ≥3x ULN and total bilirubin is ≥2x ULN, albumin and PT/INR should also be obtained.	2
9.7.8.6/Vector Shedding	If a positive result is obtained in a matrix after 3 consecutive results below the limit of detection have already been recorded, testing in that matrix should restart and continue until an additional 3 consecutive results below the limit of detection have been obtained in order to confirm clearance.	4
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: • Elevation of ALT > ULN or ~~>~~≥ 1.5x baseline value, regardless of whether that elevation triggers an initiation or modification of oral corticosteroid treatment • Events potentially meeting the criteria for Hy's law (ALT or AST elevation ≥ 3x ULN plus total bilirubin ≥ 2x ULN)	2, 15
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/or concomitantly administered corticosteroids and/or other immunosuppressive agents, and seriousness (refer to Section 10.2 for SAE definitions). ... Factors suggestive of a causal relationship could include (but are not limited to): • Absence of event prior to study drug and/or corticosteroid and/or other immunosuppressive agent exposure • Known relationship to underlying mechanism of study drug and/or corticosteroid and/or other immunosuppressive agent action • Abatement of AE with discontinuation of study drug and/or corticosteroids and/or other immunosuppressive agents, and/or recurrence of AE with reintroduction of study drug and/or corticosteroids and/or other immunosuppressive agents	6
Table 10.3.3.3.1	Table 10.3.3.3.1 has been updated to include assessment of causality against other immunosuppressive agents.	6
~~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.~~	15

Section No./Title	Revision	Rationale
10.4.1.4/Abnormal Laboratory Values	Laboratory test results (including any local FVIII activity or liver 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 unless associated with an AE that has already been reported. Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF, unless the abnormal laboratory results has been reported or captured as part of an ~~underlying diagnosis~~AE that has already been reported.	15
12.2/Screening Visit	The following procedures will be performed during the Screening Period: • Screen for COVID-19 (local or central testing) o COVID-19 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing.	1
12.2.1/Smart Rescreening Visit	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: • Screen for COVID-19 (local or central testing) o COVID-19 RT-PCR testing is required during smart rescreening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing.	1
12.4/Day 1 Visit	The following procedures will be performed during the BMN 270 Infusion Visit: • Complement panel (should be collected 2 hours after completion of the infusion)	12
12.5.15/Week 26	At Week 26~~,~~ (± 2 weeks), the following optional procedure will be performed: • Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)	15
12.6.9/Week 52	At Week 52~~,~~ (± 2 weeks), the following optional procedure will be performed: • Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)	15

Section No./Title	Revision	Rationale
12.7/Years 2-5	Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.	5
12.7.1/Year 2 (Every 4 Weeks) or Years 3-5 (every 6 Weeks) (not required for treatment failure subjects)	During Years 2 (every 4 weeks ± 2 weeks) or Years 3-5 (every 6 weeks ± 2 weeks), the following procedures will be performed: • PCR of vector DNA in semen (if required) o Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear by the end of Year 1. Subjects who have not had 3 consecutive semen samples below the limit of detection by the end of Year 1 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 samples below the limit of detection 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 semen must still provide semen samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).	14
12.7.2/Years 2-5 – Every 12 Weeks and End of Year Visits (required for all subjects)	At the every 12 week and End of Year visits, the following procedures will be performed: • PCR of vector DNA in blood, saliva, urine, semen, and stools (if required) o Sample testing during Years 2-5 is not required if at least 3 consecutive samples are below the limit of detection during the Post-Infusion Follow-Up period in Weeks 1-52. ~~Subjects who have not had 3 consecutive semen samples below the limit of detection 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 samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).~~	14
16/Costs, Compensation, and Subject Injury	~~There will be no charge to study subjects to be in this study.~~ BioMarin will pay ~~all~~the full costs of the study-related tests, procedures, and treatments ~~that are part of this study~~set forth in the protocol. In addition, after IRB/IEC 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.~~	11

Section No./Title	Revision	Rationale
	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. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort related solely to the study subject's primary disease or any concurrent disease that are unrelated to this study.	

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients
Protocol Number:	270-303
Active Investigational Product:	AAV5-hFVIII-SQ
IND/European Union Drug Regulating Authorities Clinical Trials (EudraCT) Number:	IND #: 017659 2018-004616-21
Indication:	Hemophilia A
Sponsor:	BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Development Phase:	Phase 3b
Sponsor's Responsible Medical Monitor:	PI MD, MHS PI BioMarin Pharmaceutical Inc. 105 Digital Drive Novato, CA 94949
Duration of Subject Participation:	Approximately 264 weeks
Dose:	6E13 vg/kg
Study Population:	Males aged 18 or older
Date of Original Protocol:	28 February 2020
Date of Amendment 1:	15 September 2020
Date of Amendment 2:	25 May 2021

CLINICAL STUDY PROTOCOL AMENDMENT SUMMARY

Amendment 2

25 May 2021

RATIONALE AND SUMMARY OF CHANGES

A summary of major changes covered by Amendment 2 to the 270-303 protocol is provided below:

1. Changes have been made to enhance screening for potential malignancies (including hepatic cancers) and establishing baseline liver health during the Screening Period.

Rationale: The changes made include:

- Clarifying that all patients should undergo a liver ultrasound at Screening to screen for clinically significant liver disease and hepatocellular carcinoma (HCC), and that a FibroScan can also be performed at the discretion of the Investigator;
- Moving the fasting FibroTest from Day 1 to Screening for assessment of liver fibrosis.

As no current guidelines regarding HCC screening exist for AAV gene therapy recipients, the Sponsor engaged experts regarding current and recommended screening for HCC prior to administration of gene therapy. Protocol amendments contained herein were made based upon expert opinion, literature review, and evaluation of best practices.

2. Changes have been made to enhance screening for potential malignancies (including hepatic cancers) after dosing with BMN 270.

Rationale: The changes made include:

- Including a targeted liver ultrasound at the End of Year visits for Year 1 through Year 5 to screen for HCC (additional interim liver ultrasounds may be performed at the discretion of the Investigator);
- Recommending genomic analyses for any malignancy (except non-melanoma skin cancer) diagnosed during the course of the study.

Year-end liver ultrasounds are being implemented to assess the theoretical risk of HCC. While no cases of HCC have been reported in the Sponsor's AAV gene therapy non-clinical or clinical trials (more than 150 patients dosed, with some dosed more than 5 years ago), these assessments will further inform this theoretical risk.

3. Malignancy (except non-melanoma skin cancer) has been added as an Event of Special Interest (EOSI).

Rationale: The occurrence of malignancy (as above) was added as an EOSI for purposes of expedited safety reporting and additional safety monitoring.

4. HIV-positive patients (serological evidence of HIV-1 or HIV-2 infection) may now enroll in the study, provided their HIV infection is stable and well-controlled with an adequate CD4 count (>200/mm^3) and an undetectable viral load, respectively, at Screening and they are on an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART.

Rationale: HIV-positive subjects were initially included in prior BMN 270 studies. However, after an HIV-positive subject in 270-302 developed markedly elevated liver enzyme levels after receiving 4E13 vg/kg of BMN 270, out of an abundance of caution for the long-term liver health of HIV-positive patients, further enrollment of HIV-positive subjects was suspended in 270-301 (Protocol Amendment 3) and 270-302 (Protocol Amendment 3). The subject in 270-302 referenced above was receiving efavirenz and lamivudine as part of his ART regimen. Following discussion with a liver advisory board and review of the accumulated 270-301 data, efavirenz and not lamivudine has been implicated as the most likely medication that interacted with BMN 270 and contributed to the 270-302 subject's elevated liver enzyme levels. Due to its hepatotoxicity, efavirenz is considered a prohibited medication in all BMN 270 studies.

The two HIV-positive subjects on stable, non-efavirenz-containing ART regimens who were enrolled in and dosed in 270-301 study prior to Amendment 3 have been monitored closely. Following BMN 270 infusion, these subjects continued their ART as prescribed and followed routine monitoring of CD4 count and viral load. Results from 270-301 show similar safety results for the two HIV-positive subjects compared to those who are HIV-negative. The Sponsor believes that HIV infection, in and of itself, is not a contraindication to receive BMN 270 and has therefore removed the exclusion of HIV-positive subjects, as long as they are not receiving efavirenz or other potentially hepatotoxic ART in their HIV treatment regimen.

5. Language has been added concerning the use of the SARS-CoV-2 vaccines.

Rationale: Due to the worldwide SARS-CoV-2 pandemic and evolving availability and types of vaccines, language has been added to assist with timing and planning for vaccine administration. The Sponsor's recommendations reflect the risk assessment conducted on the currently available vaccines and guidance from multiple health agencies, and include information regarding different types of SARS-CoV-2 vaccines.

6. The reactive corticosteroid regimen for ALT elevation has been updated.

Rationale: The guidance for the reactive corticosteroid regimen, including management of ALT elevations and corticosteroid taper, reflects the data gathered from previous BMN 270 studies. This change attempts to promote the safe and effective use of reactive corticosteroids.

7. Thrombin generation assay (TGA) assessment has been removed.

Rationale: Assessment of TGA in other studies in the BMN 270 development program has provided sufficient data; additional assessments are not expected to be needed. Removing this assessment helps to alleviate patient and site burden. If TGA assessments from 270-303 are needed in the future, backup aliquots from other platelet-poor plasma samples can be utilized.

8. Frequency of testing of FVIII antigen BDD Assay (hFVIII protein assay) has been decreased.

Rationale: Assessment of the hFVIII protein assay in other studies in the BMN 270 development program will provide robust characterization of transgene specific activity (ie, ratio of FVIII coagulation activity to FVIII protein expression). As subjects enrolled in this study are not expected to have different hFVIII specific activity findings, reducing the number of these assessments is acceptable and helps alleviate patient and site burden.

9. AAV5 transduction inhibition (TI) assessment after Year 1 has been modified. AAV5 TI will be assessed through Year 1, then again at the end of the study (either the End of Year visit for Year 5, or the Early Termination Visit as applicable).

Rationale: The most significant information from this assessment is obtained from baseline and samples collected shortly after dosing. As the TI remains high after dosing, there is no need to continue to track frequently more than a year after infusion.

10. Timepoints for exploratory assessment of Grp78 have been limited to Screening, Baseline, and at the time of a liver biopsy.

Rationale: Longitudinal measurement of Grp78 from an exploratory study testing whether levels of plasma Grp78 correlate with FVIII activity or ALT rise in plasma have not revealed significant correlations.

11. The timeframe for assessment of secondary efficacy endpoints concerning annualized bleeding rate (ABR) and exogenous FVIII utilization has been changed from Week 5-52 post-infusion to Week 5 to last visit by data cutoff, to align with a similar change made for Study 270-301.

12. Additional minor changes have been made for consistency and clarity.

Refer to Section 25 for a summary of revisions to Amendment 1 (dated 15 September 2020).

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 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients		
PROTOCOL NUMBER: 270-303		
STUDY SITES: Approximately 15 sites worldwide.		
PHASE OF DEVELOPMENT: Phase 3b		
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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 includes 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 and/or subcutaneous injection of a bi-specific monoclonal antibody, emicizumab, as prophylaxis 1-4 times per month. 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 annualized bleeding rate [ABR] of 1-4 with prophylaxis treatment in a recently published retrospective observational study 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 and between 20-60 in 6 prospective		

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:

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. While emicizumab prophylaxis has yielded lower bleed rates compared to prior FVIII prophylaxis, it does not physiologically recapitulate the coagulation system, requires chronic, life-long therapy, and still necessitates the use of episodic FVIII concentrates for treatment of breakthrough bleeds. 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.

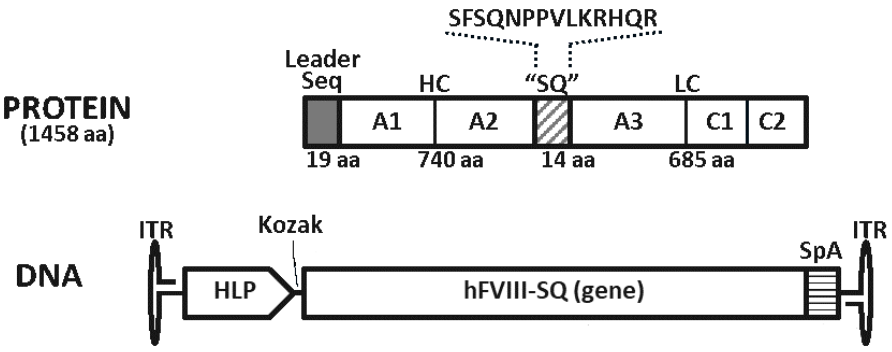
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. HA is well-suited for a gene replacement approach because clinical 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 6.7 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.

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 and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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 vector genomes [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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive).

Four-year results from 270-201 and one-year results from 270-301 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile. Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm dose-dependent pan-lobular and otherwise healthy liver transduction at 2.7-4.1 years.

Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were scheduled to start corticosteroids by Week 3 (either before Week 3, in response to an alanine aminotransferase (ALT) elevation, or at Week 3 otherwise, per

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:

protocol), whereas in 270-301 subjects received corticosteroids only in response to an ALT elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion and showed later onset of first ALT elevations when compared with subjects in 270-301. Recently published data from 270-201 and recent analysis of 270-301 data suggest that corticosteroids may have assisted in rescue or protection of FVIII activity levels during elevations of ALT and in resolution of elevated ALT levels in some subjects.

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

OBJECTIVES:

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

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:

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

The safety objectives of the study are to:

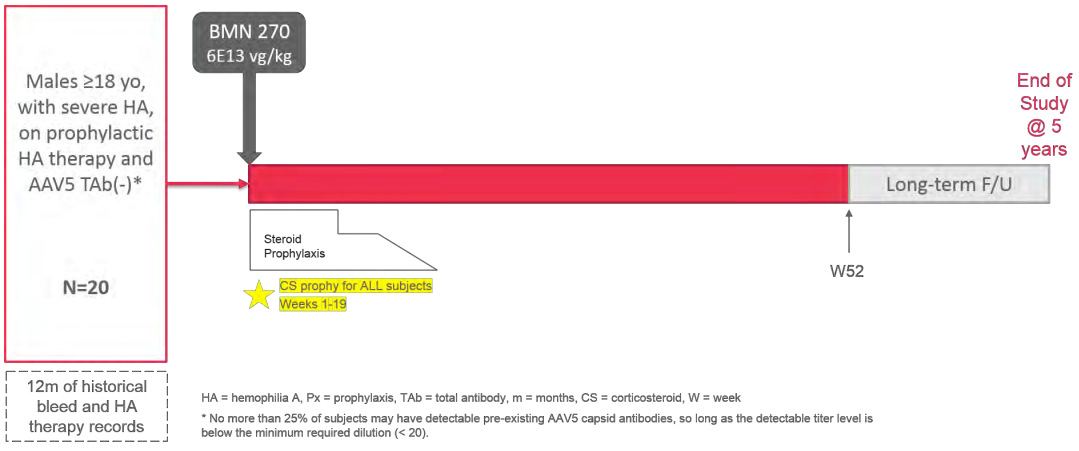
- Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids following intravenous infusion of BMN 270
- Assess the long-term safety of BMN 270 with prophylactic corticosteroids

STUDY DESIGN AND PLAN:

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 15 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of BMN 270 infusion (Figure 2). Reactive corticosteroids, as needed for ALT elevations, will also be utilized post-infusion.

Figure 2: 270-303 Study Schema



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:

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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure, manifesting as failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 and 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values and if needed, consultation with the Investigator and the Medical Monitor. Reactive oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management

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:

decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

Additionally, 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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

NUMBER OF SUBJECTS PLANNED:

Approximately 20 subjects will be enrolled into the study, with at least 16 AAV5 TAb-negative and up to 25% AAV5 total antibodies (TAb) detectable but below the minimum required dilution.

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 hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
3. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs).

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:

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 viral vector DNA below the limit of detection.
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. Subjects with detectable pre-existing antibodies to the AAV5 capsid are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies with titer level below the minimum required dilution (< 20).
2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, except for HIV infection. HIV-positive patients who meet all other eligibility criteria may be included if they have a CD4 count > 200/mm^3 and an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted) while receiving an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART.
3. Significant liver dysfunction with any of the following abnormal laboratory results:
   - ALT (alanine aminotransferase) > 1.25x upper limit of normal (ULN);
   - AST (aspartate aminotransferase) > 1.25x ULN;
   - GGT (gamma-glutamyltransferase) > 1.25x ULN;
   - Total bilirubin > 1.25x ULN;

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:

- 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. Most recent, prior FibroScan or liver biopsy showing significant fibrosis of 3 or 4 as rated on a scale of 0-4 on the Batts-Ludwig or METAVIR 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.
8. Liver cirrhosis or other clinically significant liver disease of any etiology as assessed by liver ultrasound/FibroScan.
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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.

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:

16. 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 corticosteroid treatment and/or the use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.
19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

<u>Optional Liver Biopsy Inclusion and Exclusion Criteria</u>

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

1. Able to sign informed consent and comply with requirements for the optional liver biopsy
2. Documentation of FVIII activity level ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist or radiologist, would make liver biopsy contraindicated. This includes (but is not limited to): abnormalities detected on liver ultrasound performed within 28 days of procedure or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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 6E13 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 from baseline in the annualized utilization (IU/kg/year) and infusion rate (number/year) of exogenous FVIII replacement therapy from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis. • Change from baseline in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis • Change from baseline in the total score of Haemo-QoL-A at Week 52 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:

Tertiary efficacy endpoints:

- Change from baseline in the EQ-5D-5L score at Week 52 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 post-BMN 270 infusion.
- Change from baseline in Patient Reported Outcomes, Burdens, and Experiences (PROBE) score at Week 52 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, stool, saliva)
- Liver tests (LTs, including ALT, AST, GGT, lactate dehydrogenase [LDH], total bilirubin, and alkaline phosphatase)
    - 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.
- Immune response to FVIII transgene product and AAV5 capsid proteins
- Immunological assessments, including hFVIII TAb, interferon gamma (IFNg) ELISpot, complement, and an exploratory biomarker panel.

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.

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:

STATISTICAL METHODS:

Sample Size

Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects with an AAV5 antibody titer that is detectable but below the minimum required dilution (<20) at Screening.

For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

Analysis Population

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

Subjects with an AAV5 antibody titer detectable but below the minimum required dilution will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post-BMN 270 infusion.

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. Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels ≤ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose FVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 IU/dL, and the confidence intervals of the proportions will also be provided.

The analyses of the secondary and tertiary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to 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:

- For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy from Week 5 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately, for subjects receiving prior emicizumab prophylaxis, change from baseline in the annualized utilization (mg/kg/year) of emicizumab from Week 27 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis)
- For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy from Week 5 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately for subjects receiving prior emicizumab prophylaxis, change from baseline in the annualized utilization (mg/kg/year) of emicizumab from Week 27 post BMN 270 to last visit by data cutoff (for Week 52 analysis) infusion
- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis from baseline

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

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.

The final analysis for the study will be performed after all subjects have been followed for 52 weeks post-BMN 270 infusion (or have discontinued study participation prior to Week 52).

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

Details of the planned analyses will be specified in the SAP.

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	Terms
AAV	adeno-associated virus
ABR	annualized bleeding rate
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BPV	BioMarin Pharmacovigilance
BU	Bethesda Unit
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CL	clearance
cNBA	FVIII chromogenic Nijmegen Bethesda Assay
CRA	clinical research associate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
ED	exposure days
EDC	electronic data capture
EMA	European Medicines Agency
EOSI	events of special interest
ETV	early termination visit
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FVIII	coagulation factor VIII
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HA	hemophilia A
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

Abbreviations	Terms
HIPAA	Health Insurance Portability and Accountability Act
HLP	hybrid human liver-specific promoter
IB	investigator's 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
IFNg	interferon gamma
IND	Investigational New Drug (application)
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LT	liver test
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MN	mobile nursing
NSAID	non-steroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PEG	polyethylene glycol
PK	pharmacokinetics
PRO	patient-reported outcome
PROBE	Patient Reported Outcomes, Burdens, and Experiences
rhFVIII	recombinant human FVIII
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SOI	Statement of Investigator
SOP	standard operating procedure
SQ	SFSQNPPVLKRHQR
SUSAR	serious unexpected suspected adverse reactions
TAb	total antibody

Abbreviations	Terms
TI	transduction inhibitor
ULN	upper limit of normal
vg	vector genomes
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) 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 will be provided to BioMarin or its designee. The Investigator will provide the IRB/IEC 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 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 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 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 ICF, in compliance with ICH E6 (Section 4.8), 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. BioMarin and the IRB/IEC 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 (Iorio 2019). 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 2020); 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 hybrid human liver-specific transcription promoter (HLP). 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 intravenous (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 European Medicines Agency (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

Ongoing clinical studies for BMN 270 include:

- 270-201, a phase 1/2, dose-escalation study in patients with severe HA
- 270-203, a phase 2 study in patients with severe HA who have anti-AAV5 antibody titers
- 270-301, a phase 3 study in patients with severe HA who receive BMN 270 at the 6E13 vector genomes [vg]/kg dose level
- 270-302, a phase 3 study in patients with severe HA who receive BMN 270 at the 4E13 vg/kg dose level

A comprehensive review of safety, efficacy, and immunogenicity results from these studies 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 normal (< 1 IU/dL), moderate disease comprises 1-5% of normal 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 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.

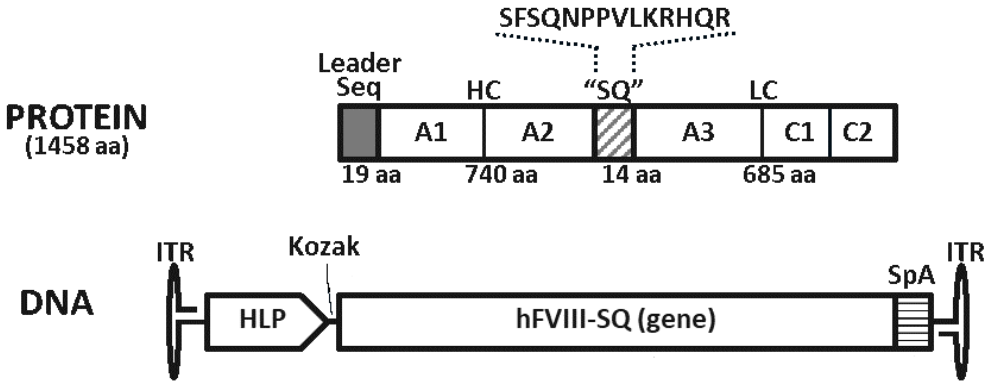
Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following a single intravenous infusion of a vector encoding the appropriate gene sequence for long-term episomal expression. Hemophilia A is well-suited for a gene replacement approach 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 6.7years; Nathwani, 2018) 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 and Encoded Protein



Legend –Note that schematic is not to scale; aa = amino acids; ITR = inverted terminal repeat; HLP = human liver promoter; Kozak = Kozak concensus sequence (GCCACC); SpA = Synthetic poly(A) signal

BMN 270 will be delivered by a single intravenous dose and is designed to achieve durable 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. Additional studies have been undertaken at the 6E13 vg/kg dose (270-301 in subjects with

severe HA, and 270-203 in subjects with severe HA who are also AAV5-antibody positive). With the exception of 270-203, subjects in other BMN 270 studies who are AAV5-antibody positive have been excluded. In 270-303, up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies, so long as the detectable titer level is below the minimum required dilution (< 20). It is expected that subjects with such a low detectable titer level will respond in a similar manner to subjects who are AAV5 capsid antibody negative.

Four-year results from 270-201 and one-year results from 270-301 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile. Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm dose-dependent pan-lobular and otherwise healthy liver transduction at 2.7-4.1 years.

Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were scheduled to start corticosteroids by Week 3 (either before Week 3, in response to an alanine aminotransferase (ALT) elevation, or at Week 3 otherwise, per protocol), whereas in 270-301 subjects received corticosteroids only in response to an ALT elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion and showed later onset of first ALT elevations when compared with subjects in 270-301. Recently published data from 270-201 and recent analysis of 270-301 data suggest that corticosteroids may have assisted in rescue or protection of FVIII activity levels during elevations of ALT and in resolution of elevated ALT levels in some subjects (Pasi 2020).

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

7.3.1 Optional Liver Biopsy Rationale

The usual pattern of response in hFVIII activity observed so far after administration of BMN 270 demonstrates peak expression levels during the first 6-12 months post-treatment followed by a decline to a steady-state level of expression thereafter. One of the explanations may lie in the kinetics of vector genome processing, which involves a series of steps such as DNA degradation and repair, annealing, and circularization that can result in the formation of

stable, double-stranded, circularized transgene DNA forms. It is these circularized DNA species that are thought to be associated with long-term, persistent expression of the gene product in target cells. Examination of transduced hepatocytes from subjects treated with BMN 270 in the 270-303 study will help to establish whether DNA circularization may occur and could account for the long-term hFVIII expression observed in humans.

Additionally, health of the liver after gene transduction has been monitored indirectly by periodic assessments of hepatic enzymes released into the blood stream. Transient, post-treatment elevations in ALT levels have been observed in the majority of subjects, as well as inter-subject variability in post-therapy FVIII activity levels. Neither the reasons for nor the significance of the ALT elevations or the variations in response to FVIII gene therapy are known. Moreover, the effects of BMN 270 on hepatic tissue structure and function are also currently unknown. Finally, a call to incorporate liver biopsy sub-studies into gene therapy trials for hemophilia has been issued by medical and scientific leaders in the field to help illuminate these and other questions (National Hemophilia Foundation 2019).

The purpose of this exploratory sub-study is to provide a better understanding of the long-term gene expression related to genome circularization, health of the liver, and variation in FVIII activity levels observed after gene therapy with BMN 270. With use of prophylactic corticosteroids, it is believed that there will be stable hepatic function and FVIII activity expression, with tolerance of prophylactic corticosteroid therapy and no change to the risk of thromboembolism. This sub-study aims to evaluate the effect on the liver by performing liver biopsies at approximately Week 26, Week 52, and/or during Years 2-5.

7.4 Summary of Overall Risks and Benefits

Overall, 151 subjects have received a BMN 270 infusion at one of 4 dose levels (6E12 vg/kg, 2E13 vg/kg, 4E13 vg/kg, or 6E13 vg/kg) in one of the four ongoing BMN 270 clinical studies (270-201, 270-301, 270-302, 270-203). Single infusions have been generally well tolerated by treated subjects across all investigated doses. All subjects have successfully completed their full-dose infusion of BMN 270, with no infusions requiring permanent termination prior to completion due to AEs. No deaths have been reported in any of the BMN 270 studies, and no participants discontinued from studies as a result of an AE. Frequency of adverse events decreased over time with no delayed adverse drug reactions.

Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) has been observed in most subjects administered BMN 270 shortly after dosing, with no evidence for major impacts upon liver function; no events meeting the Hy's Law criteria have been identified. Liver function remained stable over time. Across the 6E13 vg/kg cohort of 270-201 and 270-301,

subjects enrolled in 270-201 developed ALT elevation about 5.5 weeks later than subjects in 270-301, generally once the first course of corticosteroids was being tapered, and experienced lower peak elevations in ALT (75.7 U/L) than subjects in 270-301 (112.5 U/L). The difference in the ALT profile seen between the 6E13 vg/kg subjects in 270-201 and the subjects in 270-301 could be attributed to the difference in the protocol-specified corticosteroid regimens in place in those studies, including the early use of corticosteroids (ie, by Week 3 post-BMN 270 infusion). While the majority of ALT elevations responded rapidly to corticosteroids, given current interest in the field of AAV gene therapy for the use of non-steroidal approaches to managing or preventing ALT elevations, alternate non-steroidal systemic immunosuppressive agents have also been used to manage hepatic reactions where corticosteroids have proven to be ineffective or where high doses/and or prolonged exposure to corticosteroids have led to unwanted side effects. Overall, the literature and clinical experience with BMN 270 suggests that transient elevations in liver enzymes are expected following AAV-based gene therapy for the treatment for hemophilia A or B without any long-term concerns of hepatic injury (Manno 2006; Nathwani 2011; George 2016; Miesbach 2016; Pasi 2020).

Short-lived infusion reactions associated with one-time BMN 270 administration have included symptoms such as nausea, maculopapular rash, urticaria, diarrhea, watery eyes, rigors, chills, myalgia, fever, tachycardia and hypotension emerging within 24 hours of receiving BMN 270. Most infusion-related reactions were Grade 1 or Grade 2 in severity, and all events resolved, typically within 48 hours following medical management. While some cases required temporary interruption of the infusion, followed by re-initiation at a slower rate, all subjects completed their infusions. The reactions with onset during or within approximately 5 hours after the end of infusion responded to treatment with systemic antihistamines and/or corticosteroids, where administered. Infusion-related reactions were effectively mitigated by managing infusion rate and medications.

No subjects have experienced thromboembolic events or developed inhibitors to FVIII following BMN 270 infusion.

In this study, corticosteroids will be initiated prophylactically (ie, prior to any increase in ALT) on Day 1, prior to the BMN 270 infusion. Close monitoring of ALT and FVIII activity is recommended to enable early and timely initiation of reactive corticosteroid treatment (ie, in response to an increase in ALT). During reactive corticosteroid treatment, emphasis will be placed on a timely taper of the dose to limit sequelae associated with prolonged corticosteroid use.

Subjects given the 6E13 vg/kg dose in 270-201 and 270-301 have achieved mean FVIII activity above 40 IU/dL at 49-52 weeks post-infusion, with 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.

The current data available has shown an established positive benefit:risk profile for BMN 270 at the 6E13 vg/kg dosing level, although the impact of prophylactic corticosteroids requires further investigation. 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 270-303 will have a comprehensive surveillance plan that monitors LTs during the study, and elevations in LTs 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 the risks and benefits of treatment with BMN 270, refer to the current version of the Investigator's Brochure.

7.4.1 Optional Liver Biopsy Risks and Benefits

Liver biopsy is considered a safe procedure, with serious complications occurring less than once in every 10,000 procedures (Grant 2004). Although the theoretical risks of significant complications are extremely small, the main complications would include bleeding and bile leakage. Another theoretical complication is infection at the needle insertion site; the sterile technique used makes this risk extremely small.

The most common problems include mild pain and a minor decrease in blood pressure. More serious complications, such as bleeding, infection, and injury to nearby organs, are very rare, but the subject will be monitored appropriately to ensure correct management should any of these occur. Any complications related to the liver biopsy should be reported as adverse events, as outlined in Section 10. The liver biopsy is a standard investigation, and will be explained more fully by the experienced clinician performing the biopsy.

Each subject who participates in this optional sub-study will have a comprehensive pre-/post-biopsy surveillance plan according to the standard procedures at the institution. Timing of the liver biopsies will occur at Weeks 26, 52, and/or during Years 2-5. Safety will be assessed by adverse event reporting and clinical laboratory assessments. Per the Investigator's discretion and/or according to local guidelines, the subject may be kept in overnight following the liver biopsy for additional safety monitoring; such an overnight stay would not be considered a hospitalization for serious adverse event (SAE) reporting purposes (refer to Section 10.4.1.6).

There is no direct benefit from participating in this study other than contributing to understanding the mechanism of action of BMN 270. Consenting into this specific sub-study is optional and will not have any effect on the subject's continued participation in 270-303.

8 STUDY OBJECTIVES

The primary efficacy objective of the study is to:

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

The secondary efficacy objectives of the study are to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis
- Assess the impact of BMN 270 with prophylactic corticosteroids on quality of life as measured by the Haemo-QoL-A questionnaire at Week 52 of the study compared to baseline

The tertiary efficacy objective of the study is to:

- Assess the impact of BMN 270 with prophylactic corticosteroids on patient-reported outcomes (PROs) (other than Haemo-QoL-A) at Week 52 of the study compared to baseline

The exploratory efficacy objective of the study is to:

- Assess the efficacy of BMN 270 with prophylactic corticosteroids defined as FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52, following intravenous infusion of BMN 270 for subjects with detectable AAV5 total antibodies below the minimum required dilution at Screening

The safety objectives of the study are to:

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

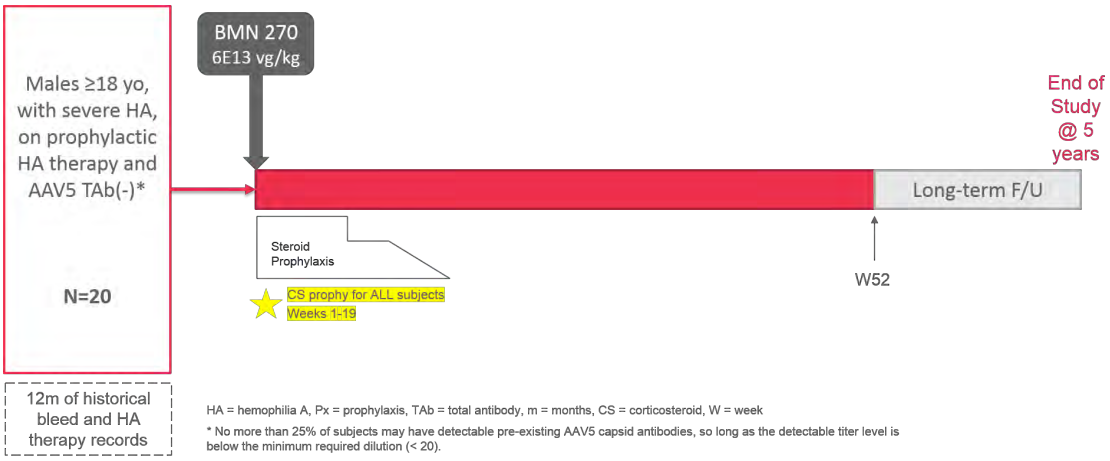
9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately 15 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. Post-infusion, subjects will be eligible to receive reactive corticosteroids, as indicated (Figure 9.1.1).

Figure 9.1.1: 270-303 Study Schema



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, will be convened. The DMC will have 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 should be paused to enable modification of the protocol or discontinued.

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

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Four weeks represents the time by which endogenous production of FVIII following gene transfer is expected to be efficacious, based on prior study results. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. Subjects who do not respond to BMN 270 treatment (ie, treatment failure manifesting as failure to achieve FVIII activity ≥ 5 IU/dL by Week 52 and 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and as indicated, consultation with the Investigator and the Medical Monitor. Reactive oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor (refer to Section 9.4.8.2).

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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).

An optional liver biopsy will be performed (in subjects who consent to do so) at or around Week 26, Week 52, and/or during Years 2-5 following BMN 270 infusion. Subjects who consent to the liver biopsy will have additional assessments, including a liver ultrasound and FibroScan, and will receive prophylactic FVIII prior to the procedure, as indicated in the judgment of the Investigator, to minimize the risk of bleeding.

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 (if the subject has given written informed consent to participate in MN visits), or at the site or approved lab facility as a shortened lab draw-only visit, 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.

Schedules of events 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 the optional liver biopsy (Table 9.1.5) 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)[o]
	Screening		Smart Rescreening[m] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[n]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Informed consent	X	X[p]			
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 hemophilia therapy usage for previous 12 months (by either subject or clinical information)		X	X	X	
Distribution of subject diaries and training in their use[b]		X			
Electrocardiogram		X			
Liver Ultrasound (and FibroScan at discretion of Investigator)[c]		X			
hFVIII Assays[d]		X	X[q]	X	
hFVIII TAb		X		X	
Screen for Hepatitis B, Hepatitis C, HIV[e]		X			
SARS-CoV-2 screening (local or central)[f]		X	X		
Blood chemistry, hematology, and coagulation tests[g]		X	X	X	
Fasting lipid panel (blood triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol)					X
Fasting FibroTest		X			

Assessment	Prior to BMN 270 Infusion				BMN 270 Infusion Visit (Day 1)[o]
	Screening		Smart Rescreening[m] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[n]	
	Screening Day -42 to Day -29	Screening* (Day -28 to Day -1)			
Urine Tests[g]		X	X	X	
Liver Tests[g]		X	X	X	
AAV5 TAb Assay (CDx)[h]	X	X	X		X
Immunogenicity AAV5 TAb Assay				X	X
AAV5 TI Assay				X	X
IFNg ELISpot				X	
Plasma, PBMC, and RBC collection for exploratory biomarkers[i]				X	
Biomarker testing[i]		X			
Serum for exploratory biomarkers[j]		X			X
Exploratory CK18 and Grp78 assessment		X		X	
Haemo-QoL-A assessment				X	
EQ-5D-5L				X	
WPAI+CIQ:HS				X	
PROBE				X	
PCR of vector DNA in blood, saliva, urine, semen, and stools				X	X
Pharmacokinetics				X[r]	
BMN 270 Infusion					X
Complement Panel and Exploratory Cytokine Profiling[k]				X	X[k]
Hypersensitivity blood assessments[l]					X[l]

* 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] 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.

[c] All patients must have a liver ultrasound performed during the Screening period to screen for significant liver disease and hepatocellular carcinoma. A FibroScan may also be performed at the discretion of the Investigator.

[d] Includes baseline FVIII activity (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), coagulation exploratory assay, chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, 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).

[e] 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).

[f] SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available. If a two-step SARS-CoV-2 vaccine is being used, sites should consider using the flexible re-screen option to allow subjects to receive both doses at least 14 days prior to treatment with BMN 270 (or at least 30 days prior to treatment with BMN 270 for any live-virus vaccines). It is preferable for SARS-CoV-2 vaccination to occur prior to BMN 270 infusion. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors, and benefit/risk related to timing of vaccine administration.

[g] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.4.1 for liver tests. ABO blood typing assessment should be performed at Screening.

[h] Screening, Smart Re-screening, and Infusion Day samples will be tested using the CDx AAV5 total antibody (TAb) assay. During Screening, the CDx AAV5 TAb assay test may be done first, under a standalone informed consent form, before the main ICF for the study is signed and further screening procedures are performed. If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening. Sample collection on the day of the infusion visit must be performed before the BMN 270 infusion is given.

[i] Includes HLA genotyping and FVIII genotyping.

[j] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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 will be performed only as deemed necessary by the Sponsor.

[k] Complement panel should include C3, C3a, C4, Bb, and sC5b-9 (refer to Table 9.7.8.2.1) and should be collected 2 hours after completion of the infusion. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor.

[l] In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for optional exploratory cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

[m] 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. SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. 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.

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

[o] With the exception of the collection of samples for polymerase chain reaction (PCR) vector DNA analysis and the collection of the complement panel/exploratory cytokine profiling sample, 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 analysis (blood, saliva, urine, semen, stool) should be collected between 2 and 24 hours after the infusion has been completed.

[p] If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

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

[r] Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

Table 9.1.2: Schedule of Events-Post-Infusion Follow-Up (Week 1-20)

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	**2[f]**	**3[f]**	**4**	**5[f]**	**6[f]**	**7[f]**	**8**	**9[f]**	**10[f]**	**11[f]**	**12**	**13[f]**	**14[f]**	**15[f]**	**16**	**17[f]**	**18**	**19[f]**	**20**
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
Physical examination[a]				X				X				X				X		X		X
Weight				X				X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs				X				X				X				X				X
Blood chemistry, hematology, and coagulation tests[b]				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	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hFVIII protein assay				X				X				X				X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	X			X				X				X				X				X
Immunogenicity AAV5 TAb Assay				X				X								X				
AAV5 TI Assay				X				X								X				
hFVIII TAb				X				X				X				X				X
IFNg ELISpot		X				X				X				X				X		
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]	X			X				X				X						X		
Complement Panel and Exploratory Cytokine Profiling[b]	X	X		X				X				X				X				X

Assessment	Follow-Up After BMN 270 Infusion – Weeks																			
	1	**2[f]**	**3[f]**	**4**	**5[f]**	**6[f]**	**7[f]**	**8**	**9[f]**	**10[f]**	**11[f]**	**12**	**13[f]**	**14[f]**	**15[f]**	**16**	**17[f]**	**18**	**19[f]**	**20**
Study Day[*]	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113	120	127	134	141
Serum for exploratory biomarkers[e]	X	X		X		X		X		X		X				X				X
Exploratory CK18 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Haemo-QOL-A assessment				X								X								
EQ-5D-5L				X								X								
WPAI+CIQ:HS				X								X								
PROBE				X								X								
Testing for reactivation of hepatitis B and hepatitis C						X[g]														X[g]

[*] Visit windows are ± 48 hours.

[a] Brief physical examination should be done at scheduled visits. Additional physical exams may be done at the discretion of the PI.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.4.1 for liver tests (LTs). LT assessment is weekly, but may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator. Subjects with ALT > ULN or ≥ 1.5x 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: the ALT has increased to ≥ 1.5x baseline value or >ULN or after a discussion between the Medical Monitor and the Investigator based on a review of subject data. If 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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, and coagulation exploratory assay. Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level will be tested as deemed necessary by the Sponsor. 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Collection and testing of semen samples must continue at least through Week 12, even if 3 consecutive results below the limit of detection in that compartment have already been recorded.

[e] Blood samples will be collected 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 any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

Table 9.1.3: Schedule of Events – Post-Infusion Follow-Up (Weeks 21-52)

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	**22**	**23[f]**	**24**	**25[f]**	**26**	**28**	**30[f]**	**32**	**34[f]**	**36**	**40**	**44**	**48**	**50[f]**	**52**
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Physical examination[a]		X		X		X	X		X		X	X	X	X		X
Weight						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	X	X	X	X
Vital Signs				X		X			X		X	X	X	X		X
Blood chemistry, hematology, and coagulation tests[b]						X			X		X		X			X
Urine Tests[b]						X					X					X
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hFVIII assays[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hFVIII protein assay				X		X			X		X	X	X	X		X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]						X			X		X		X			X
Immunogenicity AAV5 TAb Assay						X					X					X
AAV5 TI Assay						X					X					X
hFVIII TAb				X		X					X					X
IFNg ELISpot		X		X		X					X					X
Plasma, PBMC, and RBC collection for exploratory biomarkers[e]		X				X	X				X		X			X
Complement Panel and Exploratory Cytokine Profiling[b]				X		X					X					X
Serum for exploratory biomarkers[e]				X		X					X					X
Exploratory CK18 assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment	Follow-Up After BMN 270 Infusion-Weeks															
	21[f]	22	23[f]	24	25[f]	26	28	30[f]	32	34[f]	36	40	44	48	50[f]	52
Study Day[*]	148	155	162	169	176	183	197	211	225	239	253	281	309	337	351	365
Haemo-QOL-A assessment						X										X
EQ-5D-5L						X										X
WPAI+CIQ:HS						X										X
PROBE						X										X
Testing for reactivation of hepatitis B and hepatitis C									X[g]							
Optional liver biopsy[h]						X										X
Liver ultrasound[i]																X

[*] Visit windows are ± 48 hours.

[a] Brief physical examination should be done at all visits where a physical examination is indicated except Week 26 and Week 52, where a complete physical examination should be performed Additional physical exams may be done at the discretion of the PI.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.4.1 for liver tests (LTs). LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator. Subjects with > ULN or ≥ 1.5x 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: the ALT has increased to ≥ 1.5x baseline value or >ULN 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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor.

[c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, and coagulation exploratory assay. Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level will be tested as deemed necessary by the Sponsor. 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 results below the limit of detection are obtained; longer collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator.

[e] Blood samples will be collected 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 any other exploratory assessments) will be performed only as deemed necessary by the Sponsor.

[f] Visits between scheduled clinic visits 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 or approved lab facility 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. Unscheduled visits may also be conducted by MN as appropriate.

[g] Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

[h] Optional liver biopsy should be obtained within two weeks of Week 26. Additional follow-up liver biopsy will be obtained within two weeks of Week 52. Subjects should fast for at least 8 hours prior to liver ultrasound and optional liver biopsies.

[i] Additional liver ultrasounds may be performed prior to Week 52 at the discretion of the Investigator.

Table 9.1.4: Schedule of Events-Post-Infusion Follow-Up (Year 2-Year 5)

Assessment	Years 2-5*			End of Year Visit				ETV
	Years 2-5	Year 2	Year 3-5	Year 2	Year 3	Year 4	Year 5	
Study Week[*]	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
Physical examination[b]	X			X				X
Weight[b]	X[a]			X[a]				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and hemophilia therapy use)	X	X	X	X				X
Vital Signs	X			X				X
Blood chemistry, hematology, and coagulation tests[c]	X[a]			X[c]				X
Urine Tests[c]	X[a]			X[c]				X
Liver Tests[c]	X	X	X	X				X
hFVIII assays[d]	X	X	X	X				X
hFVIII protein assay	X			X				X
PCR of vector DNA in blood, saliva, urine, and stools	(X)[e]			(X)[e]				(X)[e]
PCR of vector DNA in semen	(X)[e]	(X)[e]	(X)[e]	(X)[e]				(X)[e]
Immunogenicity AAV5 TAb Assay				X				X
AAV5 TI Assay				X[j]				X[j]
hFVIII TAb	X			X				X
IFNg ELISpot[a]	X[a]			X				X
Plasma, PBMC, and RBC collection for exploratory biomarkers[f]	X			X				X
Serum for exploratory biomarkers[f]	X			X				X
Exploratory CK18 assessment	X	X	X	X				X
Haemo-QoL-A assessment	X[a]			X[a]				X
EQ-5D-5L	X[a]			X[a]				X

Assessment	Years 2-5*			End of Year Visit				ETV
	Years 2-5	Year 2	Year 3-5	Year 2	Year 3	Year 4	Year 5	
Study Week*	Q12W	Q4W[g]	Q6W[g]	W104	W156	W208	W260	
WPAI+CIQ:HS	X[a]			X[a]				X
PROBE	X[a]			X[a]				X
Optional liver biopsy[h]				X				
Liver ultrasound[i]				X				

* Visit windows are ± 2 weeks for visits in Years 2-5.

[a] These assessments need to be performed only at every other Q12W and every End of Year visit (ie, Weeks 76, 104, 128, 156, 180, 208, 232, and 260).

[b] Complete physical examination should be performed at the End of Year visits (genitourinary examination may be deferred); 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.

[c] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.4.1 for liver tests. LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator. Subjects with ALT > ULN or ≥ 1.5x 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: the ALT has increased to ≥ 1.5x baseline value or >ULN 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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

[d] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, coagulation exploratory assay. Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level will be tested as deemed necessary by the Sponsor. 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.

[e] Sample testing during Years 2-5 is not required if at least 3 consecutive samples were below the limit of detection during Year 1; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. Subjects who have not had 3 consecutive semen samples below the limit of detection 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 samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

[f] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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 will be performed only as deemed necessary by the Sponsor.

[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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage. Such subjects following the abbreviated schedule who have not yet cleared vector shedding in semen 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. Unscheduled visits may also be conducted by MN as appropriate.

[h] An optional liver biopsy may be performed at any time between Years 2-5 of the study. The optional biopsy would be triggered by a FVIII activity decline by > 50% from steady-state, over 2 consecutive measurements, or by a sustained ALT rise > ULN. If neither trigger is observed, the optional biopsy should be performed at the end of Year 5.

[i] Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the Investigator.

[j] AAV5 TI Assay should be performed only at the end of the study (either the Year 5 End of Year Visit, or at the ETV for subjects who withdraw prior to the end of Year 5).

Table 9.1.5: Schedule of Events-Optional Liver Biopsy

	Within 28 Days Before Biopsy Day	Within 7 Days Before Biopsy Day	Biopsy Day (BD)
Informed Consent for Liver Biopsy Procedure	X		
Liver Ultrasound[a]	X		
Physical examination	X		X
Hematology, Coagulation, Chemistry Assessments[b]	X		X
Liver Tests[b]	X		X
FibroScan	X		
FVIII Activity Level Assessment (central and local)		X	X[*]
Exploratory CK18 and Grp78 assessment		X	X[*]
Pre-Biopsy Consultation[c]		X	
Liver Biopsy[d]			X
PBMC Collection (whole blood draw)			X[e]

[*] If the Day -7 and biopsy day visits occur on the same day, these tests do not need to be duplicated.

[a] Liver ultrasound must be performed within 28 days prior to the scheduled biopsy. Subjects should fast for at least 8 hours prior to liver ultrasound.

[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.4.1 for liver tests.

[c] Subjects will undergo a pre-biopsy consultation with the Investigator (treating hematologist) and hepatologist and/or radiologist.

[d] Subjects should fast for at least 8 hours prior to optional liver biopsy. Biopsy will be a percutaneous or transjugular biopsy under ultrasound guidance, performed according to the standard procedure of the institution. If only a small amount of tissue (< 2 cm) is obtained at the time of the biopsy, the subject may be asked to consent for a second pass. In this case, the original < 2 cm sample should still be retained and handled according to the instructions for handling biopsy specimens in the Laboratory Manual. Following completion of the biopsy, the subject should remain in the hospital under observation for at least 4-6 hours. Overnight post-procedure observation may be done at the Investigator's discretion.

[e] Blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

Table 9.1.6: Suggested Schedule of Events-Prophylactic Corticosteroids

	Corticosteroid Treatment Period[b]																			Post-Corticosteroid Period[c]				
		Week																		Week				
Assessment	**D1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**32**
Prophylactic corticosteroid dose (mg/day)	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg	35 mg	35 mg	30 mg	30 mg	25 mg	25 mg	20 mg	20 mg	15 mg	10 mg	5 mg					
FVIII activity testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Liver tests	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis B testing[d]							X														X				X
HCV Viral Load[d]							X														X				X

[a] This table provides an example of a prophylactic corticosteroid course. Clinical judgment, weighing the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses, and discussions between the Investigator and Medical Monitor are advised for any questions or concerns. Dosages are for prednisone or an equivalent dose of another corticosteroid. FVIII and liver tests are also reflected in the Schedule of Events for the study.

[b] Following initiation or completion of corticosteroid regimen, if a recurrence of ALT values > ULN or ≥ 1.5x 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 timing of ALT elevation (prior to or after Week 52), as well as possible confounders for the ALT elevation and adverse events related to corticosteroid dosing. Guidance for tapering oral corticosteroid dosing can be found in Section 9.4.8.2, although a discussion between the PI and Medical Monitor should take place prior to tapering the corticosteroid dose.

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

[d] Should only be performed in subjects with a history of hepatitis B or hepatitis C prior to study entry. Tests are also reflected in the Schedule of Events for the study.

9.2 Discussion of Study Design

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

Given that BMN 270 is likely a one-time treatment, due to antibody formation against the AAV5 capsid post-infusion, and the well-characterized clinical experience of patients with severe hemophilia A on currently available chronic therapies, having a separate control group in this study was deemed to be inappropriate and unnecessary, as has been the case with all AAV gene therapy trials to date.

Approximately 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a prophylactic corticosteroid regimen. Post-infusion, subjects will be eligible to receive reactive corticosteroids, as indicated.

9.3 Selection of Study Population

Approximately 20 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 hemophilia therapy for at least 12 months prior to study entry. High-quality, well-documented historical data concerning bleeding episodes and hemophilia therapy usage over the previous 12 months must be available.
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 viral vector DNA below the limit of detection.
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. Subjects with detectable pre-existing antibodies to the AAV5 capsid are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies with titer level below the minimum required dilution (< 20).
2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, except for HIV infection. HIV-positive patients who meet all other eligibility criteria may be included if they have a CD4 count > 200/mm^3 and an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted) while receiving an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART.
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. FibroScan or 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 or other clinically significant liver disease of any etiology as assessed by FibroScan or 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. History of arterial or venous thromboembolic events (eg, deep vein thrombosis, non-hemorrhagic stroke, pulmonary embolism, myocardial infarction, arterial embolus), with the exception of catheter-associated thrombosis for which anti-thrombotic treatment is not currently ongoing.
14. Known inherited or acquired thrombophilia, including conditions associated with increased thromboembolic risk, such as atrial fibrillation.
15. 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.

16. 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 and/or use of alternative immunosuppressive agents outlined in the protocol) and/or would impact or interfere with evaluation and interpretation of subject safety or efficacy result.
17. Prior treatment with any vector or gene transfer agent.
18. Major surgery planned in the 52-week period following the infusion with BMN 270.
19. Use of systemic immunosuppressive agents, not including corticosteroids, or live vaccines within 30 days before the BMN 270 infusion.
20. 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.
21. Known allergy or hypersensitivity to BMN 270 investigational product formulation.
22. Unwilling to receive blood or blood products for treatment of an adverse event and/or a bleeding episode.

9.3.2.1 Optional Liver Biopsy Inclusion and Exclusion Criteria

Individuals eligible for the optional liver biopsy must meet the following inclusion criterion:

1. Able to sign informed consent and comply with requirements for the optional liver biopsy
2. Documentation of FVIII activity ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion) within 24 hours prior to the liver biopsy being performed (FVIII activity levels should be assessed at the local laboratory). Subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII levels activity to an appropriate level, under the supervision/instruction of the Investigator.

Individuals who meet any of the following exclusion criteria will not be eligible for the optional liver biopsy:

1. Any condition that, in the opinion of the Investigator or a hepatologist/radiologist would make liver biopsy contraindicated. This includes (but is not limited to) abnormalities detected on liver ultrasound performed within 28 days of procedure, or prior liver ultrasound result within 90 days that would preclude safe performance of the biopsy.

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.

Subjects may be considered lost to follow-up if the subject has missed 3 consecutive visits in the study and has failed to communicate a reason for this to the site. In addition, the site has documented at least 4 attempted contacts by key research personnel to reach the subject without success in the following manner:

- 2 attempts by telephone or email (if possible); then
- If telephone/email contacts are unsuccessful, 2 attempts must be made by certified letter or by appropriate local process.

Where communication has been made by phone, this should be documented in the subject source notes.

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. 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 electronic case report form (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, and 260 weeks of post-infusion 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

BMN 270 is a sterile, clear, colorless-to-pale yellow solution for IV infusion and is supplied in a 10 mL Crystal Zenith® (CZ) vial. Each vial contains 8.5 mL (extractable volume 8 mL) of AAV5-hFVIII-SQ at a concentration of 2E13 vector genomes per mL in a pH 7.4 phosphate buffer.

The IP 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 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.

BMN 270 will be prepared and infused as a pure solution over a dose-dependent time. Prepared drug will be kept at room temperature prior to administration. Refer to the Pharmacy Manual for IP administration instructions.

BMN 270 will be infused through the catheter using an appropriate infusion pump at an initial rate of 1 mL/min. The infusion rate should be increased every 30 minutes by 1 mL/min up to a maximum of 4 mL/min, provided that the subject's clinical condition permits such an increase. Of note, the IP has been shown to be stable at room temperature for 10 hours following completion of product thaw. 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 after an infusion-related reaction. At the restart, the infusion rate may be adjusted (ie, to a slower rate [minimum of 1 mL/min], with the rate increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min, if the subject's clinical condition permits such an increase) with careful monitoring of the subject. In the event of an infusion rate reaction with more than one dosing interruption, the infusion rate would not go beyond 1mL/min.

In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood

samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for optional exploratory cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor. Exploratory biomarker samples at baseline and at post-infusion study visits may also be used to assess changes in these biomarkers to better elucidate the mechanisms of infusion-related hypersensitivity reactions. Inpatient 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; inpatient observation can be extended beyond 8 hours if needed per Investigator discretion. After the observation period, subjects will be discharged from the clinic unless toxicity has been observed in which case the stay in the clinic may be extended 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 20 subjects will be enrolled into the single arm study of 6E13 vg/kg with prophylactic corticosteroids. Up to 25% of the total number of patients dosed should have an AAV5 antibody titer that is detectable but below the minimum required dilution (<20) at Screening.

9.4.6 Selection of Dose Used in the Study

Data from previous human studies (270-201, 270-301) indicated that dosing at 6E13 vg/kg showed improvement in FVIII activity, bleeding episodes, and exogenous FVIII utilization and infusion rate. Dosing was well tolerated, with mild increases in ALT as the most common adverse event. Please refer to the IB for detailed efficacy and safety data.

This dose is expected to be safe and effective based on clinical experience to date in 270-201 and 270-301, as well as non-clinical data.

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. For HIV-positive patients, prior to enrollment, the Medical Monitor will review the patient's ART regimen to assess that it does not contain efavirenz or another potentially hepatotoxic ART. 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 as needed (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 other than BMN 270
- Fitusiran
- Concizumab
- Efavirenz

The following medications and agents 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, including isotretinoin and dextroamphetamine/amphetamine
- Medications which may reduce or increase the plasma concentration of corticosteroids

Subjects should be counseled to avoid starting potentially hepatotoxic therapies and to inform the Investigator of any new medications prescribed by other physicians. Investigators should carefully consider both the mechanism of action and potential hepatotoxicity of any new medication prior to initiation. If a potentially concerning new medication is started, Investigators should closely monitor both FVIII activity and ALT levels (eg, weekly to every 2 weeks for the first month) in order to determine if any detrimental effects on the efficacy or safety of BMN 270 have occurred. If co-medications are required during the course of the study, where possible, please check the National Center for Biotechnology Information LiverTox website for potential hepatotoxicity issues prior to prescribing (NCBI 2020).

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

It is preferable for SARS-CoV-2 vaccination to occur prior to BMN 270 infusion. If a two-step SARS-CoV-2 vaccine is being used, sites should consider using the flexible re-screen option to allow subjects to receive both doses at least 14 days prior to treatment with BMN 270. If a live-virus SARS-CoV-2 vaccine is being used, subjects should wait at least 30 days after vaccination to receive a BMN 270 infusion. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors, and the benefit/risk related to timing of vaccine administration. Administration of SARS-CoV-2 vaccine after BMN 270 infusion may occur after consultation between Investigator and Medical Monitor.

The following medications should be avoided during oral corticosteroid therapy:

- Vaccines
- Non-steroidal anti-inflammatory drugs (NSAIDs)

9.4.8.1 Concomitant Hemophilia Treatments

To avoid breakthrough bleeding, subjects will only discontinue exogenous prophylactic FVIII replacement therapy 4 weeks following infusion of BMN 270 or if FVIII activity has consistently increased above 5 IU/dL, whichever is earlier. Subjects previously receiving emicizumab, given its approximate 1-month half-life, will remain on emicizumab prophylaxis until BMN 270 infusion, with their final dose administered prior to Day 1.

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 Investigator 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 Corticosteroid Treatment and/or Alternative Immunosuppressive Agent Treatment of Elevated Hepatic Transaminases

Prior to dosing, all subjects must be screened per steroid prescription guidelines to ensure the subject is eligible to receive corticosteroid treatment as outlined in the protocol. Refer to corticosteroid prescription guidelines for recommended monitoring for, and management of, potential side effects of corticosteroids, including guidance on medications that should be avoided during corticosteroid treatment.

9.4.8.2.1 Prophylactic Corticosteroids

All subjects will be started on prophylactic corticosteroids starting on the day of infusion (Day 1). The first dose of prophylactic corticosteroids (40 mg of prednisone or prednisolone, or an equivalent dose of another corticosteroid) should be taken at least 3 hours prior to the start of the BMN 270 infusion and continued on a daily basis. Table 9.1.6 provides the recommended prophylactic corticosteroid course, including taper and post-corticosteroid additional monitoring of FVIII activity, LTs, and hepatitis B/hepatitis C reactivation. Clinical judgment, weighing the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses. Discussions between the Investigator and Medical Monitor are advised for any questions or concerns.

9.4.8.2.2 Reactive Corticosteroids

Following initiation or completion of the prophylactic corticosteroid regimen, if ALT levels become increased (eg, ≥ 1.5x baseline value or > ULN) and alternative etiologies have been ruled out, prompt institution of newly administered or an increased dose of reactive (ie, started in response to an ALT elevation) oral corticosteroids (prednisone or an equivalent dose of another corticosteroid) should be considered after consultation with the Medical Monitor (refer to **Error! Reference source not found.**).

- Whenever possible, a confirmatory lab draw for ALT should be performed within 72 hours, along with FVIII activity, prior to initiating reactive oral corticosteroids.
- Newly administered corticosteroids or dose increases are not indicated if elevations in ALT are clearly not related to BMN 270 (eg, elevated ALT with concurrent increase in CPK due to intensive exercise) although this should be discussed with the Medical Monitor.
- Alternative immunosuppressive agents may also be considered for use on a case-by-case basis and following consultation with the Medical Monitor (eg, if prolonged corticosteroid use is contraindicated).

Unless otherwise indicated, reactive corticosteroid treatment should be initiated at a dose of 60 mg/day. If the ALT level remains stable or declines after 2 weeks, consider gradual taper of corticosteroids: 40 mg/day for 3 weeks, 30 mg/day for 1 week, 20 mg/day for 1 week and 10 mg/day for 1 week. Should a scenario arise in which differences from the minimum recommended dose and/or duration of reactive corticosteroids may be clinically indicated, a discussion should take place between the Investigator and Medical Monitor regarding corticosteroid dose adjustments. Management of ALT elevations with reactive corticosteroids, including tapering of doses and managing worsening and/or recurrent ALT elevations, should be guided by the following (Table 9.4.8.2.2.1):

Table 9.4.8.2.2.1: Management of ALT Elevations with Reactive Corticosteroids

ALT ≥ 1.5x Baseline or > ULN	• Repeat LTs and FVIII within 24-72 hours • Continue to monitor LTs until ALT is stable or not increasing • Investigate for alternative etiologies (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.) • If no alternative etiology is found, initiate reactive corticosteroids with the following tapering schedule: 60 mg x 2 weeks; 40 mg x 3 weeks; 30 mg x 1 week; 20 mg x 1 week; 10 mg x 1 week upon consultation with the Medical Monitor • Consider evaluation with additional liver tests (including but not limited to ALT, AST, bilirubin, and alkaline phosphatase) • Consider obtaining other possibly relevant laboratory evaluations (albumin, PT/INR, CRP, etc.) • Consider obtaining complete blood count with differential to assess for eosinophilia • Consider obtaining PBMC, C3, C3a, Bb, and sC5b-9 to evaluate potential immune response (prior to starting reactive oral corticosteroids) • Continue to taper as long as subject's ALT is not increasing. Decisions regarding regimen modification may be made based upon Investigator judgement and discussion with the Medical Monitor • For any ALT elevations that begin after 52 weeks on study, please consult the Medical Monitor prior to initiating corticosteroids unless there is an imminent safety concern
Worsening ALT	If after 2 weeks ALT levels have worsened with corticosteroid dose of 60 mg/day, the following is recommended: • Investigate for alternative etiologies including labs noted above, if not previously checked • Increase corticosteroid dose up to a maximum of 1.2 mg/kg for no more than 2 weeks • For subjects who are refractory to the maximum dose of corticosteroids, or intolerant to use of corticosteroids, consider use of alternative immunosuppressants (tacrolimus or mycophenolate) • Consider gastroenterology and/or hepatology consult, abdominal workup, imaging (including MRI or ultrasound), and/or liver biopsy as appropriate Any concerns should be discussed between the Investigator and the Medical Monitor
Recurrent ALT elevations	If the subject has recurrent ALT elevations (≥ 1.5x Baseline or > ULN) and there are no safety concerns, the decision regarding management may be made at the discretion of the Investigator after discussion 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.

When ruling out alternative viral or autoimmune hepatitis as part of the elevated ALT workup, the following tests should be performed (Table 9.4.8.2.2.2):

Table 9.4.8.2.2.2: Viral and Autoimmune Hepatitis Testing

Viral Hepatitis Workup PCR 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	

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

Following completion of prophylactic oral corticosteroids, if increased ALT levels (eg, > ULN or ≥ 1.5x baseline value) are 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 SoA. 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). Alternative, non-steroidal systemic immunosuppressive agents may be used, following a discussion between the Investigator and the Medical Monitor, should corticosteroid use be deemed by an Investigator to be clinically ineffective, not tolerated, and/or contraindicated. Hepatitis B status and HCV viral load will be rechecked 6 weeks after the start of oral corticosteroid/immunosuppressive agent treatment and then 1 week and 13 weeks after the completion of oral corticosteroid/immunosuppressive agent 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/immunosuppressive agent use) should be reported as outlined in Section 10 of the protocol.

Subjects on corticosteroids should receive appropriate counseling and support regarding side effects from the Investigator or the treating institution (eg, listings of side effects and when to notify carers, wallet card for emergencies if on steroids, etc.). Additional management, including the co-prescription of additional medications to prevent complications related to corticosteroid therapy, may be undertaken at the discretion of the Investigator, including, but not limited to, prophylaxis against the occurrence of gastric ulcers, osteoporosis, and infections. The above guidance should also be followed in the event that an alternative immunosuppressive agent is used, as applicable.

9.4.8.3 Monitoring of HIV-Positive Subjects

HIV-positive subjects may be enrolled in 270-303 if the subject is well controlled on an ART regimen that does not contain efavirenz or another potentially hepatotoxic ART, has a CD4 count > 200/mm^3, and has an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted).

HIV-positive subjects were initially included in prior BMN 270 studies. However, after an HIV-positive subject in 270-302 developed markedly elevated liver enzyme levels after receiving 4E13 vg/kg of BMN 270, out of an abundance of caution for the long-term liver health of HIV-positive patients, further enrollment of HIV-positive subjects was suspended in 270-301 (Protocol Amendment 3) and 270-302 (Protocol Amendment 3). The subject in 270-302 referenced above was receiving efavirenz and lamivudine as part of his ART regimen. Following discussion with a liver advisory board and review of the accumulated 270-301 data, efavirenz and not lamivudine has been implicated as the most likely medication that interacted with BMN 270 and contributed to the 270-302 subject's elevated liver enzyme levels. Due to its hepatotoxicity, efavirenz is a prohibited medication in all BMN 270 studies.

The two HIV-positive subjects on stable, non-efavirenz-containing ART regimens who were enrolled in and dosed in 270-301 study prior to Amendment 3 have been monitored closely. Following BMN 270 infusion, these subjects continued their ART as prescribed and followed routine monitoring of CD4 count and viral load. Results from 270-301 show similar safety results for the two HIV-positive subjects compared to those who are HIV-negative. The Sponsor believes that HIV infection, in and of itself, is not a contraindication to receive BMN 270 and has therefore removed the exclusion of HIV-positive subjects.

Subjects should continue ART as prescribed and follow routine monitoring of CD4 count and viral load (US Dept Health Human Services 2019). Investigators will continue to monitor HIV-positive subjects per routine standard of care.

9.4.9 Treatment Compliance

IP 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 IP containers.

9.5 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP 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 standard operating procedures (SOPs).

9.5.1 Return and Disposition of Clinical Supplies

Unused IP 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 IP or study materials (or must be referenced in their institution SOPs).

Unused IP may be destroyed on site, per the site's standard operating procedures, but only after BioMarin has granted approval for drug destruction. The study monitor must account for all IP in a formal reconciliation process prior to IP destruction. All IP 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 IP appropriately, the site can return unused IP to BioMarin upon request. The return of IP or IP materials must be accounted for on a IP return form provided by BioMarin.

All IP 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 starting at the time of informed consent for study participation and for the first 52 weeks of the study, and particularly within 48 hours prior to lab work. Alcohol use should be minimized throughout the remaining duration of the study.

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 blood and semen samples, respectively. Subjects should also abstain from organ donation.

9.7 Safety and Efficacy Variables

9.7.1 Safety and Efficacy Measurements Assessed

The Schedule of Events (Table 9.1.1 through Table 9.1.4) 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.

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 the end of 16 weeks after BMN 270 infusion and who have not resumed FVIII replacement therapy.

Note that fluctuations in FVIII activity after gene therapy are common, and more frequent monitoring of FVIII activity levels is not needed in the absence of a concurrent or recent ALT elevation or upon consultation between the Investigator and the Medical Monitor.

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 include:

- Change in the annualized utilization (IU/kg/year) and infusion (number/year) rates of exogenous FVIII replacement therapy from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) from the baseline number and utilization of exogenous FVIII replacement therapy for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change in administration of exogenous FVIII replacement therapy from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis.
- Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis, compared to the baseline ABR during the 12 months prior to study entry.

Subjects must have high quality documented historical data available concerning previous bleeding episodes and hemophilia treatment 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 will be encouraged to discuss any bleeding episodes with the Investigator and attempt to objectively assess any reported bleeds through use of ultrasound or non-invasive imaging.

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 or use of emicizumab.

9.7.3.2 Patient-Reported Outcome (PRO) Measures

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).

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.

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).

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).

Details (including sample copies where applicable) for each of the PRO instruments are provided in the Investigator Site File Binder.

9.7.4 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 chromogenic 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.

9.7.5 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.

9.7.6 Pharmacokinetics

Sparse FVIII activity assessments, prior to BMN 270 administration, will be collected to estimate each subject's half-life of replacement FVIII concentrate used for prophylaxis. Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. If supported by the data, sparse samples together with established population pharmacokinetic models will be used to estimate an individual subject's FVIII activity clearance (CL) value. Individual subject CL estimates may then be evaluated against post-BMN 270 FVIII activity levels to determine if an association exists between an individual's FVIII activity CL value and FVIII activity levels achieved with BMN 270. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

9.7.7 Exploratory Assessments

Blood samples will be collected from subjects at the time points indicated in the Schedules of Events 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.

9.7.7.1 Optional Liver Biopsy

Subjects electing to undergo an optional liver biopsy are required to consent to the procedure and collection of tissue in the study ICF. The analysis of the optional liver biopsy is considered exploratory. Patients who elect to proceed will have a liver biopsy performed around Week 26, Week 52, and/or during Years 2-5. Additional liver biopsies at times deemed to be clinically relevant (eg, decreasing FVIII at a time of increased ALT) may be pursued. Subjects will be asked to consent to the procedure for each liver biopsy performed during the study.

Subjects who consent to the procedure will have a liver biopsy via either transjugular or percutaneous (ultrasound-guided) route, according to the standard procedures of the institution. Two tissue cores will be harvested in the context of the optional liver biopsy. Subjects will be required to observe an 8-hour fasting period before the procedure.

Within 24 hours prior to the biopsy being performed, subjects must have a documented FVIII activity level of ≥ 50 IU/dL (or higher, depending on local guidelines and/or Investigator discretion). FVIII activity levels for this purpose should be assessed at the local laboratory within 7 days before the biopsy and again on the day the biopsy, prior to the procedure. As needed, subjects may be treated with additional exogenous FVIII replacement products in order to increase their FVIII activity levels to an appropriate level, under the supervision/instruction of the Investigator, to ensure the safety of the subject during the procedure. This exogenous FVIII usage (if performed) should be recorded in the eCRF FVIII infusion pages under the category “Surgery/Procedure”.

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5
Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests

- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- Local FVIII activity level assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the Investigator's discretion and/or according to local guidelines.

Clinically significant findings reported from the histopathological analysis of the biopsy sample are subject to AE reporting (Section 10). Such findings should be further assessed and followed as clinically appropriate to manage the subject's medical care. A hepatologist and/or other specialist clinicians should be consulted if required. In the event that fibrotic changes are observed on the biopsy sample, additional liver ultrasound, FibroScan and/or Enhanced Liver Fibrosis (ELF) testing (as regionally available and/or approved by HA) may be considered at the discretion of the Investigator and/or hepatologist.

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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched

sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample

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.

In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample.

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	**Complement Panel**
CPK	Differential cell count	Protein	C3
Creatinine	RBC indices (MCV and MCH)	Glucose	C3a
CRP		Bilirubin	C4
Glucose		Nitrite	Bb
Phosphorus		Urobilinogen	sC5b-9
Potassium		Hemoglobin	
Total protein			**Other Tests:**
Sodium			ABO blood typing*
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 at Screening.

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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for optional exploratory cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.

At applicable sites, certain study assessments may be performed by an 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 at the visits indicated in the Schedules of Events. Unscheduled visits may also be conducted by MN as appropriate.

9.7.8.3 Malignancies

A liver ultrasound (and FibroScan, at the discretion of the Investigator) will be performed at Screening to screen for hepatocellular carcinoma (HCC). Thereafter, liver ultrasounds will be performed annually at each End of Year visit starting at Year 1 (Week 52) through the end of the study to screen for HCC, or at interim timepoints at the discretion of the Investigator.

Any development of a malignancy (except non-melanoma skin cancers) during the course of the study will be considered an EOSI (refer to Section 10.2.1) and is subject to expedited reporting. In addition, it is recommended that genomic analyses be performed on any malignancy (except non-melanoma skin cancers) diagnosed during the course of the study. The study site will coordinate sending samples from the malignancy for genomic analyses if available.

9.7.8.4 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 negative surface antigen or DNA for hepatitis B or negative 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 the timepoints listed in Table 9.1.6. 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.

A liver ultrasound, fasting FibroTest, and liver tests (LTs) during Screening will be performed to assess for clinically significant liver disease and HCC. A FibroScan may also

be performed during Screening at the discretion of the Investigator. Fasting FibroTest results must be available prior to BMN 270 infusion.

Where a biopsy has been taken for safety-related reasons or was available from a past procedure, the Sponsor may request the biopsy information to help evaluate the impact of BMN 270 on the liver. The Sponsor may request that slides from a liver biopsy be made available for additional histopathological review.

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

Table 9.7.8.4.1: 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 plan outlined in Table 9.4.8.2.2.1 (note that these evaluations may indicate additional testing of LTs and FVIII levels at unscheduled visits; these unscheduled laboratory tests may be completed by a mobile nursing professional at sites where the use of MN services has been approved).

9.7.8.5 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. Refer to Section 9.4.8.3 for guidance on monitoring of HIV-positive subjects.

9.7.8.6 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 the timepoints indicated in the schedules of events. 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 should be performed during Screening/Baseline, at Week 26 (± 2 weeks) 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.

A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. The genitourinary examination may be deferred for visits after Year 1 unless the subject has genitourinary-related complaints.

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 at the timepoints indicated in the Schedules of Events.

9.7.8.7 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. Testing will continue until at least 3 consecutive results below the limit of detection are obtained; additional collection and testing may be performed based on batch testing schedules, result turnaround times, or discussions between Medical Monitor and Investigator. If a positive result is obtained in a matrix after 3 consecutive results below the limit of detection have already been recorded, testing in that matrix should restart and continue until an additional 3 consecutive results below the limit of detection have been obtained in order to confirm clearance.

Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point.

Subjects who have not had 3 consecutive semen samples below the limit of detection by Week 52 should continue to have PCR testing in semen every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until 3 consecutive samples below the limit of detection are documented (or upon consultation between the Investigator and Medical Monitor).

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, stool). 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, after consultation between the Medical Monitor and the Investigator, 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 below the limit of detection for vector DNA on at least three consecutive visits.

Contraception use may need to be extended beyond 12 weeks in individual subjects based on observed vector shedding in semen. After 12 weeks, subjects may stop contraception use only if they have had 3 consecutive semen samples below the limit of detection (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.

  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 > ULN or ≥ 1.5x baseline value, regardless of whether that elevation triggers an initiation or modification of oral corticosteroid treatment
- Events potentially meeting the criteria for Hy's law (ALT or AST elevation ≥ 3x ULN plus total bilirubin ≥ 2x ULN)
- Thromboembolic event
- Immediate reactions: infusion-related reactions, hypersensitivity adverse events, or anaphylaxis
- Development of anti-FVIII inhibitory antibodies (inhibitors)
- Any new diagnosis of malignancy (except non-melanoma skin cancer)

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/or concomitantly administered corticosteroids and/or other immunosuppressive agents, 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 Common Terminology Criteria for Adverse Events (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/or corticosteroids and/or other immunosuppressant agents 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 and/or corticosteroids and/or other immunosuppressive agents has not occurred **OR** • The administration of the IP and/or corticosteroids and/or other immunosuppressive agents 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 and/or corticosteroids and/or other immunosuppressive agents; that is, there are no facts, evidence, or arguments to suggest a causal relationship to the IP and/or corticosteroids and/or other immunosuppressive agents.
Related	• The administration of the IP and/or corticosteroids and/or other immunosuppressive agents and the occurrence of the AE are reasonably related in time **AND** • The AE could not possibly be explained by factors or causes other than exposure to the IP and/or corticosteroids and/or other immunosuppressive agents **OR**
	• The administration of IP and/or corticosteroids and/or other immunosuppressive agents and the occurrence of the AE are reasonably related in time **AND** • The AE is more likely explained by exposure to the IP and/or corticosteroids and/or other immunosuppressive agents 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 and/or corticosteroid and/or other immunosuppressive agent exposure
- Consistency with study product pharmacology
- Known relationship to underlying mechanism of study drug and/or corticosteroid and/or other immunosuppressive agent action
- Similarity to adverse reactions seen with related drug products

- Abatement of AE with discontinuation of study drug and/or corticosteroids and/or other immunosuppressive agents, and/or recurrence of AE with reintroduction of study drug and/or corticosteroids and/or other immunosuppressive agents

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 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.

10.4.1.3 Abnormal Laboratory Values

Laboratory test results (including any local FVIII activity or liver 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 unless associated with an AE that has already been reported.

Any laboratory result abnormality of CTCAE Grade 4 or 5 should be recorded as an SAE in the AE eCRF, unless the abnormal laboratory results has been reported or captured as part of an AE that has already been reported.

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).

10.4.1.4 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).

10.4.1.5 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a pre-existing condition (refer to Section 10.4.1.4). 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.

10.4.1.6 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

10.4.1.7 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.

10.4.1.8 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 BioMarin Pharmacovigilance (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 electronic data capture (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 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 of becoming aware of the event.

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: PI
Fax: PI
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: PI, MD, MHS
Address: 105 Digital Drive
Novato, CA 94949 USA
Phone: PI
E-mail: PI

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.

During the first part of the Screening Period (Day -42 to Day -29), testing for AAV5 TAb titers using the CDx screening assay may be performed, so that subjects can verify their AAV5 TAb status. Subjects who agree to participate in this activity may be asked to sign a separate ICF documenting this decision. Subjects who do not have testing during this period will have CDx AAV5 TAb testing along with the rest of the Screening assessments.

If the subject underwent early AAV5 TAb testing and was consented using the full study ICF, the ICF does not need to be re-administered and re-signed as part of regular Screening. If the subject underwent early AAV5 TAb testing and was consented using the dedicated stand-alone ICF for that purpose, the full ICF will need to be signed if the subject proceeds to regular Screening.

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, hepatitis C, or HIV will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or episodic hemophilia 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 Investigator Site File Binder.
- Distribution of subject diaries and training in diary completion
- Electrocardiogram
- Liver ultrasound to screen for HCC and clinically significant liver disease (FibroScan can be performed additionally at the discretion of the Investigator)
- 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)
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - hFVIII protein assay (collected but not tested prior to enrollment)
- hFVIII total antibody (TAb) assay (collected but not tested prior to enrollment)
- 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.
- SARS-CoV-2 screening (local or central testing)
    - SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available (refer to Section 9.4.8).
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
    - ABO blood typing assessment should be performed at Screening
- Urine tests (refer to Table 9.7.8.2.1)
- Liver tests (refer to Table 9.7.8.4.1)
- AAV5 TAb Assessment (CDx)

  - If performed during the early Screening period, the CDx AAV5 TAb assessment does not need to be repeated as part of general Screening

- Fasting FibroTest
  - Subjects will fast for at least 8 hours prior to sampling on the day of the FibroTest Screening visit. Fasting FibroTest results must be available prior to BMN 270 infusion.
- Biomarker testing (including HLA genotyping and FVIII genotyping status)
- Serum for exploratory biomarkers
- Exploratory CK18 and Grp78 assessment

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))
- 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 9.7.8.4.1)

- SARS-CoV-2 screening (local or central testing)
    - SARS-CoV-2 RT-PCR testing is required during smart rescreening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available (refer to Section 9.4.8).
- AAV5 TAb Assessment (CDx)

12.3 Baseline Visit

Baseline values will be recorded from 1 to 7 days prior to the treatment visit. Subjects are considered enrolled into the study once the Baseline visit has occurred. 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)
- 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
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level
    - hFVIII protein assay
- hFVIII TAb
- 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 9.7.8.4.1)
- Immunogenicity AAV5 TAb assay
- AAV5 TI assay
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Complement Panel and Exploratory Cytokine Profiling

- Exploratory CK18 and Grp78 assessment
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE
- PCR of vector DNA in blood, saliva, urine, semen, and stools
- Pharmacokinetics
    - Samples will be drawn immediately prior to recombinant FVIII concentrate infusion (between Day -2 and Day -7), 3 hours (+/- 30 minutes) post-FVIII infusion, and 24-52 hours post-FVIII infusion. For subjects receiving emicizumab, pharmacokinetics assessment is optional.

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:

- Initiation of prophylactic corticosteroids (at least 3 hours prior to BMN 270 infusion)
- Brief physical examination (prior to 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.
- Assessment of adverse events and concomitant medications (prior to infusion)
- 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.
- AAV5 TAb Assay (CDx) (sample collected pre-infusion for analysis)
- Immunogenicity AAV5 TAb Assay (sample collected pre-infusion)
- AAV5 TI Assay (sample collected pre-infusion)
- Serum for exploratory biomarkers (sample collected pre-infusion)
- BMN 270 Infusion

- Complement Panel and Exploratory Cytokine Profiling (should be collected 2 hours after completion of the infusion)
- Hypersensitivity blood assessments (if required, see below)
- 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for optional exploratory cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient 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 have weekly assessments during Weeks 1-26. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At the Week 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:

- Assessment of adverse events and concomitant medications (including review of subject diary for bleeding and FVIII use)

- Liver Tests (refer to Table 9.7.8.4.1)
    - LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator.
- Samples for FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor)
- Exploratory CK18 assessment

12.5.2 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
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Complement Panel and Exploratory Cytokine Profiling

12.5.3 Weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, and 26

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

- Serum for exploratory biomarkers

12.5.4 Weeks 2, 4, 8, 12, 16, 20, 24, and 26

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

- Complement Panel and Exploratory Cytokine Profiling

12.5.5 Weeks 2, 6, 10, 14, 18, 22, 24, and 26

At Weeks 2, 6, 10, 14, 18, 22, 24, and 26, the following procedure will be performed:

- IFNg ELISpot

12.5.6 Weeks 4, 8, 12, 16, 20, 24, and 26

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

- Vital Signs

- Weight (not done at Week 24)
- hFVIII TAb
- hFVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (not done at Week 24)
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained. Testing of semen will continue at least through Week 12, even if 3 consecutive results below the limit of detection have been recorded in that compartment prior to that time point.

12.5.7 Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26

At Weeks 4, 8, 12, 16, 18, 20, 22, 24, and 26, the following procedures will be performed:

- Brief physical examination
    - A complete physical examination should be done at Week 26.

12.5.8 Weeks 4, 8, 16, and 26

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

- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay

12.5.9 Weeks 4, 8, 12, 18, 22, and 26

At Weeks 4, 8, 12, 18, 22, and 26, the following procedure will be performed:

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.5.10 Week 4, 12, and 26

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

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

12.5.11 Weeks 4, 16, and 26

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

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

12.5.12 Weeks 12 and 26

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

- Urine Tests (refer to Table 9.7.8.4.1)

12.5.13 Weeks 6 and 20

At Weeks 6 and 20, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

12.5.14 Week 26

At Week 26 (± 2 weeks), the following optional procedure will be performed:

- Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)

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

After Week 27, subjects will have assessments at Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52. Visits between scheduled clinic visits 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 or approved lab facility 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 hemophilia therapy use. For MN visits, the service will collect this information. Unscheduled visits may also be conducted by MN as appropriate.

At these visits, the following assessments will be performed.

12.6.1 Each Visit (Weeks 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52)

The following procedures will be performed at every visit (Week 26, 28, 30, 32, 34, 36, 40, 44, 48, 50, and 52):

- Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)
- Liver Tests (refer to Table 9.7.8.4.1)
    - LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator.

- Samples for FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor)
- Exploratory CK18 assessment

12.6.2 Weeks 28, 32, 36, 40, 44, 48, and 52

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

- Brief physical examination (complete physical examination at Week 52)

12.6.3 Week 28, 36, 44, and 52

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

- Plasma, PBMC, and RBC collection for exploratory biomarkers

12.6.4 Week 32

At Week 32, the following procedure will be performed:

- Testing for reactivation of hepatitis B and hepatitis C
    - Testing for reactivation of hepatitis B and hepatitis C only for subjects with a past medical history of hepatitis B or hepatitis C prior to study entry.

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

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

- Vital Signs
- hFVIII protein assay

12.6.6 Weeks 32, 36, 44, and 52

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

- Weight
- Blood chemistry, hematology, and coagulation tests (refer to Table 9.7.8.2.1)
- PCR of vector DNA in blood, saliva, urine, semen, and stools
    - Sample testing to occur until at least 3 consecutive sample results below the limit of detection have been obtained.

12.6.7 Week 36 and 52

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

- Urine Tests (refer to Table 9.7.8.4.1)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay
- hFVIII TAb
- IFNg ELISpot
- Complement Panel and Exploratory Cytokine Profiling
- Serum for exploratory biomarkers

12.6.8 Week 52

At Week 52, the following procedures will be performed:

- Liver ultrasound
    - Additional liver ultrasounds may be performed prior to Week 52 at the discretion of the Investigator
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE

12.6.9 Week 52

At Week 52 (± 2 weeks), the following optional procedure will be performed:

- Optional liver biopsy (refer to Section 12.9 for assessments related to liver biopsy)

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 and Q6W visits during Years 2-5; 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. Unscheduled visits may also be conducted by MN as appropriate.

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 semen 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage.

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

12.7.1 Year 2 (Every 4 Weeks) or Years 3-5 (Every 6 Weeks) (not required for treatment failure subjects)

During Years 2 (every 4 weeks ±2 weeks) or 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 9.7.8.4.1)
    - LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor)
        - If a subject tests positive in the cNBA during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.

- Exploratory CK18 assessment
- PCR of vector DNA in semen (if required)
    - Sample testing during Years 2-5 is not required if at least 3 consecutive samples are clear by the end of Year 1. Subjects who have not had 3 consecutive semen samples below the limit of detection by the end of Year 1 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 samples below the limit of detection 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 semen must still provide semen samples for assessment every 4 weeks (during Year 2) or every 6 weeks (during Years 3-5) until vector shedding has cleared (in such a case, these subjects do not need to perform other assessments except for PCR sample delivery scheduled at these timepoints).

12.7.2 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 (final study visit)

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.

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 (genitourinary examination may be deferred); 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)
- Vital Signs

- 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)
- Liver Tests (refer to Table 9.7.8.4.1)
    - LT assessment may be checked more frequently when ALT values are > ULN or ≥ 1.5x baseline value or based upon discussion between the Medical Monitor and the Investigator.
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor)
        - If a subject tests positive in the cNBA during Years 3-5, a fresh sample should be collected within 4 weeks of the initial visit that had a positive result.
- hFVIII protein assay
- Immunogenicity AAV5 TAb Assay (at End of Year visits only)
- AAV5 TI Assay (at End of Year 5 visit only)
- hFVIII TAb
- Interferon gamma (IFNg) ELISpot (at Week 76, Week 128, Week 180, Week 232, and End of Year visits only)
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Exploratory CK18 assessment
- Liver ultrasound (at End of Year visits only)
    - Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the investigator
- 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)

- 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)
- 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 below the limit of detection during the Post-Infusion Follow-Up period in Weeks 1-52.
- Optional liver biopsy (Years 2-5) (refer to Section 12.9 for assessments related to liver biopsy)

12.8 Early Termination 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 ETV. The Early Termination Visit (ETV) will occur on the date the subject withdraws from the study, even if the date does not correspond to a protocol-specific visit. At the ETV, as many of the following assessments as possible should be done:

- Complete 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 9.7.8.4.1)
- FVIII Assays
    - FVIII activity level (chromogenic substrate FVIII assay)
    - FVIII activity level (one-stage clotting FVIII assay)
    - FVIII coagulation activity exploratory assay
    - Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor)
- hFVIII protein assay
- PCR of vector DNA in blood, saliva, urine, semen, and stools (if required)
- Immunogenicity AAV5 TAb Assay
- AAV5 TI Assay

- hFVIII TAb
- IFNg ELISpot
- Plasma, PBMC, and RBC collection for exploratory biomarkers
- Serum for exploratory biomarkers
- Exploratory CK18 assessment
- Haemo-QoL-A assessment
- EQ-5D-5L
- WPAI+CIQ:HS
- PROBE

12.9 Optional Liver Biopsy

Details on required procedures for the optional liver biopsy are outlined in Table 9.1.5. Subjects may be asked to provide a liver biopsy around Week 26, Week 52, and during the Years 2-5 period post-BMN 270 infusion.

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 28 days before the procedure, as follows:

- Liver ultrasound (subject should fast at least 8 hours prior to ultrasound)
- Physical examination
- Hematology, coagulation, chemistry assessments
- Liver tests
- FibroScan

Subjects consenting to participate to the optional liver biopsy will undergo pre-biopsy assessments at least 7 days before the procedure, as follows:

- FVIII activity level assessment (central and local)
- Exploratory CK18 and Grp78 assessment
- Pre-biopsy consultation (with hepatologist and/or radiologist)

On the day of the biopsy, brief physical examination and liver and blood tests should be performed before the procedure (including hematology, coagulation, and chemistry). FVIII activity assessment should also be performed to ensure the subject has sufficient FVIII activity to protect against procedure-related bleeding (as discussed above). LT assessment and a whole blood draw for PBMC collection should be performed on the biopsy day or ± 1 week from the biopsy day.

The optional liver biopsy should be performed in the morning if feasible, and the biopsy procedure and follow-up care should be done according to the local standard of care. Additional details for handling the biopsy specimens are provided in the Study Reference Manual.

Following completion of the biopsy, the subject should remain under observation in the clinic for at least 4-6 hours. Overnight post-procedure observation may be done at the Investigator's discretion and/or according to local guidelines.

12.10 End of Study

The study will end after the last subject yet to complete the Week 260 visit 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.

Sites will enter study data into eCRFs into the study EDC system. Data Quality Control will be performed by BioMarin Clinical Data Management or designee through implementation of quality control checks specified in the study data management plan and edit check specifications.

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 analyses. Unless otherwise stated, all analyses will be performed using SAS.

14.1.1 Interim Analyses

No formal interim analysis is planned. Informal analyses (ie, no hypothesis testing) may be performed at different timepoints to assess efficacy and safety over time. The primary efficacy endpoint for such analyses involves hFVIII activity, as measured by chromogenic substrate assay, and is defined as median FVIII activity during a specific 4-week time interval post-BMN 270 infusion.

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.

Missing data imputation and sensitivity analyses to assess the impact of missing data on the primary and secondary efficacy endpoints analyses are described in the following sections. 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 at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). Baseline value of 1 IU/dL (eligible subjects must have residual FVIII levels ≤ 1 IU/dL as evidenced by medical history) will be used in the calculation of change from baseline since all the subjects will be on prophylactic hemophilia therapy prior to BMN 270 infusion where the FVIII activity level cannot be reliably measured. Descriptive summaries of the proportions of subjects whose hFVIII activity during Weeks 49-52 is greater than or equal to select thresholds, such as 5, 15, 25, 30, and 40 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 14.9.

14.3 Secondary Efficacy Endpoints

The analyses of the secondary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion:

- For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy from Week 5 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately, for subjects receiving prior emicizumab prophylaxis, change from baseline in the annualized utilization (mg/kg/year) of emicizumab from Week 27 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis)
- For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy from Week 5 post BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately for subjects receiving prior emicizumab prophylaxis, change from baseline in the annualized utilization (mg/kg/year) of emicizumab from Week 27 post BMN 270 to last visit by data cutoff (for Week 52 analysis) infusion
- Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment from Week 5 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis from baseline

Mean change from baseline and associated 95% confidence interval will be calculated for the total score of Haemo-QoL-A at Week 52 post-BMN 270 infusion as well.

The missing value of the change for annualized utilization and annualized infusion rate will be imputed as 0. The missing value of the change for annualized number of bleeding episodes will be imputed using the median value of the changes of all observed cases.

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, repeated within subject. The actual

number of bleeding episodes will be used as the dependent variable with the time period adjustment (annualization) 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.

14.4 Tertiary Efficacy Endpoints

The analyses of the tertiary efficacy endpoints will be descriptive. Mean change from baseline and associated 95% confidence interval will be provided for EQ-5D-5L, WPAI+CIQ: HS and PROBE scores at Week 52 post-BMN 270 infusion.

14.5 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.

14.6 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).

14.7 Safety Analysis

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

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.

14.8 Determination of Sample Size

Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects with an AAV5 antibody titer that is detectable but below the minimum required dilution (< 20) at Screening. For the primary endpoint, a sample size of 16 will provide 85% power to demonstrate that

the change in hFVIII activity during Weeks 49-52 from baseline is greater than 0, assuming an effect size of 0.8, using a one-sample t-test at the 1-sided significance level of 0.025 (or equivalently, at the 2-sided significance level of 0.05). The effect size of 0.8 is assumed conservatively based on the results from 270-201 and the interim results from 270-301.

14.9 Analysis Populations

The intention-to-treat (ITT) population is defined as all subjects who received BMN 270 infusion. The ITT population will be the primary population for safety analyses, as well as being used for supportive efficacy analyses.

The modified intention-to-treat (mITT) population is the primary analysis population for efficacy for this study. The mITT population will include all subjects who received BMN 270 infusion and who were AAV5 antibody negative at Screening (ie, excludes subjects with an AAV5 antibody titer detectable but below the minimum required dilution).

The AAV MRD population (ie, subjects with an AAV5 antibody titer detectable but below the minimum required dilution) will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post BMN 270 infusion.

14.10 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 must be sought, and the Investigator should inform BioMarin and the full IRB/IEC within 2 working days after the emergency occurs.

With the exception of minor administrative or typographical changes, the IRB/IEC 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 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, 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 continue enrolling subjects based on emerging data and the overall risk/benefit analysis of BMN 270.
- Making other recommendations on the conduct and reporting of the trial based on their evaluation of clinical data.

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 SAP.

16 COSTS, COMPENSATION, AND SUBJECT INJURY

BioMarin will pay the full costs of the study-related tests, procedures, and treatments set forth in the protocol. In addition, after IRB/IEC approval, BioMarin may reimburse the reasonable cost of travel for study-related visits in accordance with BioMarin's travel and reimbursement policy.

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. 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. If this is the case, BioMarin will comply with the law. BioMarin will not pay for any hospitalizations, tests, or treatments for medical problems of any sort related solely to the study subject's primary disease or any concurrent disease that are unrelated to this study.

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 date and 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. When in person site monitoring or source data verification cannot be conducted, remote site monitoring and/or source data verification will be conducted where allowed by country and local health authorities and ECs/IRBs.

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. 1995;19:1409-1417.

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

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. 2012;18(Suppl.6):1-13.

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. 2016;22(Suppl.4):151-152.

Grant A, Neuberger J, Day C, Saxseena S. British Society of Gastroenterology Guidelines on the use of Liver Biopsy in Clinical Practice. 2004. Available at: https://www.bsg.org.uk/resource/bsg-guidelines-on-the-use-of-liver-biopsy-in-clinical-practice.html (last visited 20 January 2020).

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

Haemo-QoL Study Group. Scoring Manual. Available at: http://haemoqol.de/scoring/manual (last accessed 17 May 2021).

Iorio A, Stonebraker JS, Chambost H, et al, for the Data and Demographics Committee of the World Federation of Hemophilia. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-546.

Kaufman RJ, Powell JS. Molecular approaches for improved clotting factors for hemophilia 1. Blood. 2013;122(22):3568-3574.

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. 2006;12(3):342-347.

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. 2016;22(Suppl.4):151-152.

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. 2014;371(21):1994-2004.

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. 2011;19(5):876-885.

National Center for Biotechnology Information (NCBI). LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Available at: https://livertox.nih.gov (last accessed 17 May 2021).

National Hemophilia Foundation. MASAC recommendation for liver biopsies in gene therapy trials for hemophilia. 2019. Available at https://www.hemophilia.org/sites/default/files/document/files/256.pdf (last accessed 20 August 2020).

Pasi KJ, Rangarajan S, Mitchell N, Lester W et al. Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A. N Engl J Med. 2020;382(1):29-40.

Reilly M. WPAI Scoring. 2002. Available at: http://www.reillyassociates.net/WPAI_Scoring.html (last accessed 4 September 2020).

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, Santagostino E, Dougall A, Kitchen S et. al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia. 2020;26(Suppl 6):1-158.

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

United States Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2019. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (last accessed 17 May 2021).

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 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. Additionally, he or she will not make any changes in the research without IRB/EC 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 3b, Single Arm, Open-Label Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII, with Prophylactic Corticosteroids in Hemophilia A Patients

Protocol Number: 270-303 Amendment 2

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: PI MD, MHS, PI , Clinical Sciences

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):

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

   b. 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 original protocol and relates the changes to the appropriate rationale (refer to pages 2-5). Added text is indicated by underlined font and deleted text is indicated by ~~strikethrough~~ font.

Section No./Title	Revision	Rationale
2/Synopsis (Study Sites)	Approximately ~~10~~15 sites worldwide.	12
2/Synopsis (Study Rationale)	~~Three~~Four-year results from 270-~~–~~201 and one-year results from 270-301 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile. Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm dose-dependent pan-lobular and otherwise healthy liver transduction at 2.~~5~~7-4.1 years. ~~In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201.~~ Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were ~~started on~~scheduled to start corticosteroids by Week 3 (either ~~therapeutically~~before Week 3, in response to an alanine aminotransferase (ALT) elevation, or ~~prophylactically~~at Week 3 otherwise, per protocol), whereas in 270-301 subjects received corticosteroids only in response to an ~~alanine aminotransferase (~~ALT~~)~~ elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion~~,~~ and showed later ~~advent~~onset of first ALT elevations~~, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation~~ when compared with subjects in 270-301 ~~(20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity.~~. Recently published data from 270-201 ~~suggests~~and recent analysis of 270-301 data suggest that corticosteroids may have assisted in rescue or protection of FVIII activity levels during elevations of ALT and in resolution of elevated ALT levels in some subjects.	6, 12
2/Synopsis (Objectives)	The secondary efficacy objectives of the study are to: • Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis • Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis The safety objectives of the study are to:	11, 12

Section No./Title	Revision	Rationale
	• Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids ~~during the first 52 weeks~~ following intravenous infusion of BMN 270	
2/Synopsis (Study Design and Plan)	This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately ~~10~~15 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of BMN 270 infusion (Figure 2). ~~Therapeutic~~Reactive corticosteroids, as needed for ALT elevations ~~and/or FVIII decline~~, will also be ~~available~~utilized post-infusion. … In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. 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~~and 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. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values~~, FVIII activity levels,~~ and if needed, consultation with the Investigator and the Medical Monitor. ~~Therapeutic~~Reactive oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor.	6, 12
2/Synopsis (Exclusion Criteria)	Patients are excluded from the study if any of the following criteria apply: 1. Subjects with detectable pre-existing antibodies to the AAV5 capsid~~.~~ are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies~~, so long as the detectable~~ with titer level ~~is~~ below the minimum required dilution (< 20). 2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, ~~including~~except for HIV infection. HIV-positive patients who meet all other eligibility criteria may be included if they have a CD4 count > 200/mm^3 and an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted) while receiving an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART. 8. Liver cirrhosis or other clinically significant liver disease of any etiology as assessed by liver ultrasound/FibroScan.	4, 12
2/Synopsis (Criteria for Evaluation)	Secondary efficacy endpoints: • Change from baseline in the annualized utilization (IU/kg/year) and infusion rate (number/year) of exogenous FVIII replacement therapy ~~during~~from Week 5 ~~to Week 52~~ post-BMN 270 infusion~~,~~ to last visit by data cutoff (for Week 52 analysis) for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change from baseline in the annualized utilization (mg/kg/year) of emicizumab ~~during~~from Week 27 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis.	11, 12

Section No./Title	Revision	Rationale
	• Change from baseline in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) ~~during~~from Week 5 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis	
2/Synopsis (Statistical Methods)	Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects ~~who have~~with an AAV5 antibody titer that is detectable but below the minimum required dilution (<20) at Screening. The analyses of the secondary and tertiary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion: • For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy ~~during Weeks~~from Week 5 ~~52~~ post -BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately, for subjects receiving ~~FVIII~~prior emicizumab prophylaxis ~~during the 12 months prior to study entry, or,~~ change from baseline in the annualized utilization (mg/kg/year) of emicizumab ~~during~~from Week 27 ~~to Week 52~~ post -BMN 270 infusion ~~for subjects receiving prior emicizumab prophylaxis~~to last visit by data cutoff (for Week 52 analysis) • For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy ~~during Weeks~~from Week 5 ~~52~~ post -BMN 270 infusion~~,~~ to last visit by data cutoff (for Week 52 analysis); and separately for subjects receiving ~~FVIII~~prior emicizumab prophylaxis ~~during the 12 months prior to study entry, or,~~ change from baseline in the annualized utilization (mg/kg/year) of emicizumab ~~during~~from Week 27 ~~to Week 52~~ post -BMN 270 to last visit by data cutoff (for Week 52 analysis) infusion ~~for subjects receiving prior emicizumab prophylaxis~~ • Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment ~~during Weeks~~from Week 5 ~~52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or ~~Weeks~~from Week 27 ~~52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis from baseline	11, 12
7.3/Study Rationale	~~Three~~Four-year results from 270~~–~~201 and one-year results from 270-301 have demonstrated that following gene transfer, mean and median FVIII activity levels above 15% (15 IU/dL), as measured by a chromogenic substrate assay, are achievable and sustained following a single infusion of 6E13 vg/kg of BMN 270, with an acceptable safety profile ~~(Pasi, 2020).~~ Preliminary results from optional liver biopsies (in subjects receiving lower doses of BMN 270 in 270-201) confirm dose-dependent pan-lobular and otherwise healthy liver transduction at 2.5~~7~~-4.1 years. ~~In addition, an interim analysis of clinical study 270-301, an ongoing phase 3 study designed to assess the efficacy and safety of BMN 270 at a dose of 6E13 vg/kg, demonstrated FVIII activity levels that were also well above 15 IU/dL, albeit lower than what was observed for the 6E13 vg/kg cohort in 270-201 (Pasi, 2020).~~ Subjects receiving 6E13 vg/kg in 270-201 received a different corticosteroid regimen than subjects in 270-301; in 270-201, subjects were ~~started on~~scheduled to start corticosteroids by Week 3 (either ~~therapeutically~~before Week 3, in response to an alanine	6, 12

Section No./Title	Revision	Rationale
	aminotransferase ~~[~~(ALT~~]~~) elevation, or ~~prophylactically~~at Week 3 otherwise, per protocol), whereas in 270-301 subjects received corticosteroids only in response to an ALT elevation. Possibly as a result of this difference, subjects receiving 6E13 vg/kg in 270-~~-~~201 started corticosteroids at an earlier date in reference to the date of BMN 270 infusion~~,~~ and showed later ~~advent~~onset of first ALT elevations~~, and were also less likely to experience a significant decline in FVIII activity concurrently with an ALT elevation~~ when compared with subjects in 270-301~~ (20% of subjects in 270-201 vs. 58% of subjects in 270-301). In 270-301, ALT elevation within the first 26 weeks was associated with decreased FVIII activity.~~. Recently published data from 270-201 ~~suggests~~and recent analysis of 270-301 data suggest that corticosteroids may have assisted in rescue or protection of FVIII activity levels during elevations of ALT and in resolution of elevated ALT levels in some subjects (Pasi ~~,~~2020).	
7.4/Summary of Risks and Benefits	Transient, asymptomatic ALT elevation (grade 1 to 3 in severity) has been observed in most subjects administered BMN 270 shortly after dosing, with no ~~symptoms or sequelae suggestive of clinically significant hepatocyte injury or~~evidence for major impacts upon liver ~~dysfunction~~function; no events meeting the Hy's Law criteria have been identified. ~~ALT~~Liver function remained stable over time. Across the 6E13 vg/kg cohort of 270-201 and 270-301, subjects enrolled in 270-201 developed ALT elevation about 5.5 weeks later than subjects in 270-301, generally once the first course of corticosteroids was being tapered, and experienced lower peak elevations ~~have been reported as events of interest in 13 subjects in 270-201, 1 subject~~ in ~~270-302, and 91~~ALT (75.7 U/L) than subjects in 270-301~~. Although the majority of events have been Grade 1 or Grade 2~~ (112.5 U/L). The difference in ~~severity, 11~~the ALT profile seen between the 6E13 vg/kg subjects ~~(1~~ in 270-~~302~~201 and ~~10~~the subjects in 270-301~~) had a reported Grade 3 ALT elevation. Only one serious event of ALT increased has been reported~~ could be attributed to the difference in the protocol-specified corticosteroid regimens in place in those studies, including the early use of corticosteroids (ie, by ~~investigators (in addition to one event that BioMarin conservatively assessed as serious based on the details of the case~~Week 3 post-BMN 270 infusion). While the majority of ALT elevations responded rapidly to corticosteroids, given current interest in the field of AAV gene therapy for the use of non-steroidal approaches to managing or preventing ALT elevations, alternate non-steroidal systemic immunosuppressive agents have also been used to manage hepatic reactions where corticosteroids have proven to be ineffective or where high doses/and or prolonged exposure to corticosteroids have led to unwanted side effects. Overall, the literature and clinical experience with BMN 270 suggests that transient elevations in liver enzymes are expected following AAV-based gene therapy for the treatment for hemophilia A or B without any long-term concerns of hepatic injury (Manno~~,~~ 2006; Nathwani~~,~~ 2011; George~~,~~ 2016; Miesbach ~~,~~2016; Pasi~~, 2017~~ 2020). Short-lived infusion reactions associated with one-time BMN 270 administration have included symptoms such as nausea, maculopapular rash, urticaria, diarrhea, watery eyes, rigors, chills, myalgia, fever, tachycardia and hypotension emerging within 24 hours of receiving BMN 270. Most infusion-related reactions were Grade 1 or Grade 2 in severity, and all events resolved, typically within 48 hours following medical management. ~~Three of these~~While some cases required temporary interruption of the infusion, followed by re-initiation at a slower rate~~.~~, all subjects completed their infusions. The reactions with onset during or within	6, 12

Section No./Title	Revision	Rationale
	approximately 5 hours after the end of infusion responded to treatment with systemic antihistamines and/or corticosteroids, where administered. Infusion-related reactions were effectively mitigated by managing infusion rate and medications. In this study, corticosteroids will be initiated prophylactically (ie, prior to any increase in ALT) on Day 1, prior to the BMN 270 infusion. Close monitoring of ALT and FVIII activity is recommended to enable early and timely initiation of ~~therapeutic~~reactive corticosteroid treatment (ie, in response to an increase in ALT). During ~~prophylactic and therapeutic~~reactive corticosteroid treatment, emphasis will be placed on a ~~slow~~timely taper of the dose~~, with the aim of achieving ALT levels near the subject's baseline~~ to limit ~~hepatocellular toxicity and possibly ameliorate reduction of transgene expression over the period when ALT elevations have been observed~~sequelae associated with prolonged corticosteroid use. ~~At~~Subjects given the ~~highest~~6E13 vg/kg dose ~~tested~~ in 270-201 ~~(6E13 vg/kg), the majority of subjects~~and 270-301 have achieved mean FVIII activity above ~~50~~40 IU/dL at 49-52 weeks post-infusion~~. Subjects in that cohort 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.~~ ~~In 270-301, an interim analysis has shown increased FVIII activity in the majority of subjects to mild HA or normal levels at 26 weeks post-infusion, also,~~ with markedly decreased bleeding compared with pre-study rates and the ability to discontinue prophylactic FVIII infusions. ~~All subjects who will be included in the final analysis have been dosed with 6E13 vg/kg and~~Subjects at all dose levels continue to be followed.	
8/Study Objectives	The secondary efficacy objectives of the study are to: • Assess the impact of BMN 270 with prophylactic corticosteroids on the use of exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis • Assess the impact of BMN 270 with prophylactic corticosteroids on the number of bleeding episodes requiring exogenous FVIII replacement therapy from Week 5 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis or on use of emicizumab from Week 27 to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis The safety objectives of the study are to: • Evaluate the short-term safety of BMN 270 with prophylactic corticosteroids ~~during the first 52 weeks~~ following intravenous infusion	11, 12

Section No./Title	Revision	Rationale
9.1/Overall Study Design and Plan	This is a Phase 3b, single arm, open-label study in hemophilia A patients with residual FVIII levels ≤ 1 IU/dL. Subjects will be enrolled at approximately ~~10~~15 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 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a 19-week prophylactic corticosteroid regimen starting on the day of the BMN 270 infusion. Post-infusion, subjects will be eligible to receive ~~on demand~~reactive corticosteroids, as indicated. … In subjects who experience recurring bleeding episodes, the Investigator and Medical Monitor will discuss whether to resume prior FVIII prophylaxis. 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~~and 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. Subjects who are not attending the Q4W/Q6W visits during Years 2-5 may receive a scheduled monthly follow-up telephone call from the site to ask about adverse events, concomitant medications, and bleeding events/FVIII replacement usage. There will be an ongoing review of individual subject safety by the Medical Monitor, and both safety and efficacy data by the DMC. Patients will receive prophylactic corticosteroids with tapering of the dosage based upon consideration of ALT values, FVIII activity levels, and as indicated, consultation with the Investigator and the Medical Monitor. ~~Therapeutic~~Reactive oral corticosteroids may be initiated if a subject's ALT values increase from baseline levels, after consultation between the Investigator and the Medical Monitor	6, 12
Table 9.1.1 through Table 9.1.4/Schedules of Events	Tables 9.1.1, 9.1.2, 9.1.3, and 9.1.4 have been updated consistent with changes made in the table footnotes and elsewhere in the protocol.	1, 2, 5, 7, 8, 9, 10, 12
Table 9.1.1 Footnotes	[ec] All patients must have a liver ultrasound performed during the Screening period to screen for significant liver disease and hepatocellular carcinoma. A FibroScan may also be performed at the discretion of the Investigator. [e] ~~COVID-19~~f SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available. If a two-step SARS-CoV-2 vaccine is being used, sites should consider using the flexible re-screen option to allow subjects to receive both doses at least 14 days prior to treatment with BMN 270 (or at least 30 days prior to treatment with BMN 270 for any live-virus vaccines). It is	1, 5, 7, 8, 12

Section No./Title	Revision	Rationale
	preferable for SARS-CoV-2 vaccination to occur prior to BMN 270 infusion. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors, and benefit/risk related to timing of vaccine administration. [ij] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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~~, as well as testing of the thrombin generation assay (TGA) sample,~~ will be performed only as deemed necessary by the Sponsor. [jk] Complement panel should include C3, C3a, C4, Bb, and sC5b-9 (refer to Table 9.7.~~7~~8.2.1) and should be collected 2 hours after completion of the infusion. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor. [lm] 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. ~~COVID-19~~SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. 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. [no] With the exception of the collection of samples for polymerase chain reaction (PCR) vector DNA analysis and the collection of the complement panel/exploratory cytokine profiling sample, 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 analysis (blood, saliva, urine, semen, stool) should be collected between 2 and 24 hours after the infusion has been completed.	
Table 9.1.2 Footnotes	[b] Refer to Table 9.7.8.2.1for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.3.1 for liver tests (LTs). ~~LTs~~ LT assessment is weekly, but may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ~~upper limit of normal (~~ULN~~)~~ or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value~~; (2) Increases in ALT values from prior assessment are~~	6, 7, 8, 12

Section No./Title	Revision	Rationale
	~~accompanied by declines in FVIII activity level;~~ or >ULN 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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor. [c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, and coagulation exploratory assay~~, and~~. Chromogenic Nijmegen-Bethesda Assay for hFVIII ~~protein assay~~inhibitor level will be tested as deemed necessary by the Sponsor. 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. [e] Blood samples will be collected 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.	
Table 9.1.3 Footnotes	[b] Refer to Table 9.7.8.2.1 for laboratory assessments to be included and for complement panel tests, and to Table 9.7.8.4.1 for liver tests (LTs). ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value~~; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level;~~ or >ULN 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	2, 6, 7, 8, 12

Section No./Title	Revision	Rationale
	between the Medical Monitor and the Investigator. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample. While exploratory samples for cytokine profiling will be collected at the time points indicated above, testing of these samples will be performed only as deemed necessary by the Sponsor. [c] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, and coagulation exploratory assay~~, and~~. Chromogenic Nijmegen-Bethesda Assay for hFVIII ~~protein~~inhibitor level will be tested as deemed necessary by the Sponsor. 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. [e] Blood samples will be collected 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. [i] Additional liver ultrasounds may be performed prior to Week 52 at the discretion of the Investigator.	
Table 9.1.4 Footnotes	[b] Complete physical examination should be performed at the End of Year visits~~;~~ (genitourinary examination may be deferred); 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. [c] Refer to Table 9.7.8.2.1 for laboratory assessments to be included, and to Table 9.7.8.4.1 for liver tests. ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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 > ULN or ≥ 1.5x 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 ≥ 1.5x baseline value~~; (2) Increases in ALT values from prior assessment are accompanied by declines in FVIII activity level;~~ or >ULN 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	2, 6, 7, 8, 9, 11, 12

Section No./Title	Revision	Rationale
	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. In case of a safety concern, additional unscheduled laboratory tests may be performed locally (at the Investigator's discretion) in order to facilitate timely and appropriate clinical management decisions; where possible, a matched sample for testing at the central laboratory should be collected (using the Unscheduled Visit lab kit) at the same time as the local unscheduled sample [d] Includes FVIII activity level (chromogenic substrate FVIII assay and one-stage clotting FVIII assay), chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level, coagulation exploratory assay~~, and hFVIII protein assay~~. Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level will be tested as deemed necessary by the Sponsor. 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. [f] Blood samples will be collected to evaluate biochemical, molecular, cellular, immunological, 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~~, as well as testing of the TGA assay sample,~~ will be performed only as deemed necessary by the Sponsor. [i] Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the Investigator. [j] AAV5 TI Assay should be performed only at the end of the study (either the Year 5 End of Year Visit, or at the ETV for subjects who withdraw prior to the end of Year 5).	
Table 9.1.6 Footnotes	[b] Following initiation or completion of corticosteroid regimen, if a recurrence of ALT values > ULN or ≥ 1.5x 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 timing of ALT elevation (prior to or after Week 52), as well as possible confounders for the ALT elevation~~, relationship between increases in ALT and FVIII activity, ALT levels/FVIII activity post corticosteroid initiation,~~ and adverse events related to corticosteroid dosing. Guidance for tapering oral corticosteroid dosing can be found in Section 9.4.8.2, although a discussion between the PI and Medical Monitor should take place prior to tapering the corticosteroid dose.	6

Section No./Title	Revision	Rationale
9.2/Discussion of Study Design	Approximately 20 adult subjects with severe HA will receive a 6E13 vg/kg dose of BMN 270 as a single intravenous infusion in conjunction with receipt of a prophylactic corticosteroid regimen. Post-infusion, subjects will be eligible to receive ~~on-demand~~reactive corticosteroids, as indicated.	6
9.3.2/Exclusion Criteria	Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study: 1. Subjects with detectable pre-existing antibodies to the AAV5 capsid~~.~~ are excluded with the following exception: up to 25% of subjects may have detectable pre-existing AAV5 capsid antibodies~~, so long as the detectable~~ with titer level ~~is~~ below the minimum required dilution (< 20). 2. Any evidence of active infection, including COVID-19, or any immunosuppressive disorder, ~~including~~except for HIV infection. HIV-positive patients who meet all other eligibility criteria may be included if they have a CD4 count > 200/mm^3 and an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted) while receiving an antiretroviral therapy (ART) regimen that does not contain efavirenz or another potentially hepatotoxic ART. 8. Liver cirrhosis or other clinically significant liver disease of any etiology as assessed by liver ultrasound/FibroScan.	4, 12
9.4.4/Directions for Administration	In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for ~~an~~ optional~~,~~ exploratory cytokine ~~bead array (CBA)~~profiling to assess inflammatory biomarkers and plasma cytokine levels.	12
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. For HIV-positive patients, prior to enrollment, the Medical Monitor will review the patient's ART regimen to assess that it does not contain efavirenz or another potentially hepatotoxic ART. 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 as needed (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 other than BMN 270 …	4, 5, 12

Section No./Title	Revision	Rationale
	It is preferable for SARS-CoV-2 vaccination to occur prior to BMN 270 infusion. If a two-step SARS-CoV-2 vaccine is being used, sites should consider using the flexible re-screen option to allow subjects to receive both doses at least 14 days prior to treatment with BMN 270. If a live-virus SARS-CoV-2 vaccine is being used, subjects should wait at least 30 days after vaccination to receive a BMN 270 infusion. Investigators should use clinical judgment, taking into consideration local factors, individual risk factors, and the benefit/risk related to timing of vaccine administration. Administration of SARS-CoV-2 vaccine after BMN 270 infusion may occur after consultation between Investigator and Medical Monitor.	
9.4.8.2.1 Prophylactic Corticosteroids	All subjects will be started on prophylactic corticosteroids starting on the day of infusion (Day 1). The first dose of prophylactic corticosteroids (40 mg of prednisone or prednisolone, or an equivalent dose of another corticosteroid) should be taken at least 3 hours prior to the start of the BMN 270 infusion and continued on a daily basis. Table 9.1.6 provides ~~an example of a possible~~the recommended prophylactic corticosteroid course, including taper and post-corticosteroid additional monitoring of FVIII activity, LTs, and hepatitis B/hepatitis C reactivation. Clinical judgment, ~~weighting~~weighing the potential risks and benefits of corticosteroid treatment, should always be exercised when considering adjustment of corticosteroid doses. Discussions between the Investigator and Medical Monitor are advised for any questions or concerns.	6, 12
9.4.8.2.2 Reactive Corticosteroids	Following initiation or completion of the prophylactic corticosteroid regimen, if ALT levels become increased (eg, ≥ 1.5x baseline value or > ULN) and alternative etiologies have been ruled out, prompt institution of newly administered or an increased dose of ~~therapeutic or on-demand~~reactive (ie, started in response to an ALT elevation) oral corticosteroids (prednisone or an equivalent dose of another corticosteroid) should be considered after consultation with the Medical Monitor (refer to Table 9.7.8.3.2). • Whenever possible, a confirmatory lab draw for ALT should be performed within 72 hours, along with FVIII activity, prior to initiating reactive oral corticosteroids. Unless otherwise indicated, ~~therapeutic~~reactive corticosteroid treatment should be initiated at a dose of 60 mg/day. If the ALT level ~~immediately returns to ≤ 1.5x baseline and FVIII activity levels continue to rise and/~~remains stable or ~~remain within or above the normal range in the~~declines after 2 weeks ~~following corticosteroid initiation, on-demand~~, consider gradual taper of corticosteroids ~~can be discontinued. However, if this is not the case, therapeutic corticosteroids should be tapered over a longer period of time. At minimum, the recommended duration of on-demand corticosteroids is 60 mg/day for 3 weeks,~~: 40 mg/day for 43 weeks, ~~and~~ 30 mg/day for ~~4 weeks, followed by a gradual taper thereafter.~~1 week, 20 mg/day for 1 week and 10 mg/day for 1 week. Should a scenario arise in which ~~a deviation~~differences from the minimum recommended dose and/or duration of ~~therapeutic~~reactive corticosteroids may be clinically indicated, a discussion should take place between the Investigator and Medical Monitor regarding corticosteroid dose adjustments. ~~Tapering~~Management of ~~corticosteroid dosages~~ALT elevations with reactive corticosteroids, including tapering of doses and managing worsening and/or recurrent ALT elevations, should be guided by the following (Table 9.~~7~~4.8.2.1): [Table 9.4.8.2.2.1]	6, 12

Section No./Title	Revision	Rationale
	When ruling out alternative viral or autoimmune hepatitis as part of the elevated ALT workup, the following tests should be performed (Table 9.4.8.2.2): [Table 9.4.8.2.2] After discontinuation of ~~on-demand~~reactive 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~~prophylactic oral corticosteroids, if increased ALT levels (eg, > ULN or ≥ 1.5x baseline value) are 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.	
Table 9.4.8.2.2.1/ Management of ALT Elevations with Reactive Corticosteroids	Table 9.4.8.2.2.1 has been updated consistent with changes elsewhere in the protocol, and has been merged with the former Table 9.7.8.3.1.	6, 12
Table 9.4.8.2.2.2/Viral and Autoimmune Hepatitis Testing	Table 9.4.8.2.2.2 has been relocated from its previous position as Table 9.7.8.3.2.	6, 12
9.4.8.3/Monitoring of HIV-Positive Subjects	HIV-positive subjects may be enrolled in 270-303 if the subject is well controlled on an ART regimen that does not contain efavirenz or another potentially hepatotoxic ART, has a CD4 count > 200/mm^3, and has an undetectable viral load (unquantifiable viral load as defined as less than the limit of quantification by the testing laboratory's assay is permitted). HIV-positive subjects were initially included in prior BMN 270 studies. However, after an HIV-positive subject in 270-302 developed markedly elevated liver enzyme levels after receiving 4E13 vg/kg of BMN 270, out of an abundance of caution for the long-term liver health of HIV-positive patients, further enrollment of HIV-positive subjects was suspended in 270-301 (Protocol Amendment 3) and 270-302 (Protocol Amendment 3). The subject in 270-302 referenced above was receiving efavirenz and lamivudine as part of his ART regimen. Following discussion with a liver advisory board and review of the accumulated 270-301 data, efavirenz and not lamivudine has been implicated as the most likely medication that interacted with BMN 270 and contributed to the 270-302 subject's elevated liver enzyme levels. Due to its hepatotoxicity, efavirenz is a prohibited medication in all BMN 270 studies. The two HIV-positive subjects on stable, non-efavirenz-containing ART regimens who were enrolled in and dosed in 270-301 study prior to Amendment 3 have been monitored closely. Following BMN 270 infusion, these subjects continued their ART as prescribed and followed routine monitoring of CD4 count and viral load. Results from 270-301 show similar safety results for the two HIV-	4

Section No./Title	Revision	Rationale
	positive subjects compared to those who are HIV-negative. The Sponsor believes that HIV infection, in and of itself, is not a contraindication to receive BMN 270 and has therefore removed the exclusion of HIV-positive subjects. Subjects should continue ART as prescribed and follow routine monitoring of CD4 count and viral load (US Dept Health Human Services 2019). Investigators will continue to monitor HIV-positive subjects per routine standard of care.	
9.7.2.1/FVIII Activity	~~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 after gene therapy are common, and ~~if no clear trend indicating a decline in~~ more frequent monitoring of FVIII activity levels is ~~observed, then this additional testing may be deferred (~~not needed in the absence of a concurrent or recent ALT elevation or 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~~.	6, 12
9.7.3.1/FVIII Replacement Therapy/Bleeding Episodes	Secondary efficacy variables include: • Change in the annualized utilization (IU/kg/year) and infusion (number/year) rates of exogenous FVIII replacement therapy ~~during~~from Week 5 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) from the baseline number and utilization of exogenous FVIII replacement therapy~~,~~ for subjects receiving FVIII prophylaxis during the 12 months prior to study entry, or change in administration of exogenous FVIII replacement therapy from Week 27 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis. • Change in the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment (annualized bleeding rate, ABR) ~~during~~from Week 5 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or from Week 27 ~~to Week 52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis, ~~from~~compared to the baseline ABR during the 12 months prior to study entry. Subjects must have high quality documented historical data available concerning previous bleeding episodes and hemophilia treatment 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 will be encouraged to discuss any bleeding episodes with the Investigator and attempt to objectively assess any reported bleeds through use of ultrasound or non-invasive imaging.	11, 12

Section No./Title	Revision	Rationale
9.7.8.2/Clincal Laboratory Assessments	In addition to scheduled clinical laboratory assessments, a fasting blood lipid panel (including triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol) ~~and FibroTest~~ 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 a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for ~~an~~ optional~~,~~ exploratory ~~CBA~~cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.	1, 12
9.7.8.3/Malignancies	A liver ultrasound (and FibroScan, at the discretion of the Investigator) will be performed at Screening to screen for hepatocellular carcinoma (HCC). Thereafter, liver ultrasounds will be performed annually at each End of Year visit starting at Year 1 (Week 52) through the end of the study to screen for HCC, or at interim timepoints at the discretion of the Investigator. Any development of a malignancy (except non-melanoma skin cancers) during the course of the study will be considered an EOSI (refer to Section 10.2.1) and is subject to expedited reporting. In addition, it is recommended that genomic analyses be performed on any malignancy (except non-melanoma skin cancers) diagnosed during the course of the study. The study site will coordinate sending samples from the malignancy for genomic analyses if available.	1, 2, 3
9.7.8.4/Liver and Hepatitis Testing	A liver ultrasound~~/FibroScan~~, fasting FibroTest, and liver tests (LTs) during Screening will ~~identify any~~be performed to assess for clinically significant ~~hepatic dysfunction.~~ liver disease and HCC. A FibroScan may also be performed during Screening at the discretion of the Investigator. Fasting FibroTest results must be available prior to BMN 270 infusion. Elevated ALT levels (above the upper limit of normal range) should be evaluated according to the ~~following~~ plan outlined in Table 9.4.8.2.2.1.	1, 6
9.7.8.5/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. Refer to Section 9.4.8.3 for guidance on monitoring of HIV-positive subjects.	4
9.7.8.6/Vital Signs, PEs and Other Safety Observations	A complete physical examination will include general appearance (head, eyes, ears, nose, and throat), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, and neurologic systems. The genitourinary examination may be deferred for visits after Year 1 unless the subject has genitourinary-related complaints.	12
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:	3

Section No./Title	Revision	Rationale
	• Any new diagnosis of malignancy (except non-melanoma skin cancer)	
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 Common Terminology Criteria for Adverse Events (NCI CTCAE) ~~v5~~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 ~~v5as~~v4.03 as stated in Table 10.3.3.2.1.	12
10.8/Urgent Safety Measures	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 of becoming aware of the event.	12
12.2/Screening	The following procedures will be performed during the Screening Period: • Full medical history, including hemophilia A history, hepatitis B, hepatitis C, and HIV. Subjects with a history of hepatitis B ~~or,~~ hepatitis C, or HIV will be asked for information about the treatments received. Any prior pharmacokinetics information obtained while the subject was receiving prophylactic or ~~on demand~~episodic hemophilia therapy prior to the study should also be collected. • Liver ultrasound~~/~~ to screen for HCC and clinically significant liver disease (FibroScan can be performed additionally at the discretion of the Investigator) • ~~Screen for COVID-19~~SARS-CoV-2 screening (local or central testing) o ~~COVID-19~~SARS-CoV-2 RT-PCR testing is required during Screening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available (refer to Section 9.4.8). • Fasting FibroTest o Subjects will fast for at least 8 hours prior to sampling on the day of the FibroTest Screening visit. Fasting FibroTest results must be available prior to BMN 270 infusion.	1, 4, 5, 12
12.2.1/Smart Rescreening	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: • ~~Screen for COVID-19~~SARS-CoV-2 screening (local or central testing)	5

Section No./Title	Revision	Rationale
	○ ~~COVID-19~~SARS-CoV-2 RT-PCR testing is required during smart rescreening, and all subjects must have at least one negative test result prior to dosing. If the test is performed locally an additional 2nd test is recommended, but if performed negative results from the 2nd test must be received prior to dosing. A SARS-CoV-2 vaccine is recommended for subjects if indicated and if available (refer to Section 9.4.8).	
12.3/Baseline	The following procedures will be performed during the Baseline Period: • Complement Panel and Exploratory Cytokine Profiling • ~~TGA Assay~~	7, 12
12.4/Day 1	The following procedures will be performed during the BMN 270 Infusion Visit: • Brief physical examination (prior to infusion) • Assessment of adverse events and concomitant medications (prior to infusion) • ~~Fasting FibroTest~~ • Immunogenicity AAV5 TAb Assay (sample collected pre-infusion) • AAV5 TI Assay (sample collected pre-infusion) • Serum for exploratory biomarkers (sample collected pre-infusion) • Complement Panel and Exploratory Cytokine Profiling (should be collected 2 hours after completion of the infusion) In case of a Grade 2 or higher hypersensitivity or adverse drug reaction, a safety assessment including physical examination and vital signs will be performed and additional blood samples will be collected within 1 hour, and 8-24 hours following the hypersensitivity reaction for assessment of complement (C3, C3a, C4, Bb, and sC5b-9) and tryptase. Additional samples will be collected at the 1 hour and 8-24 hour time points and, if possible, 1 week after the event for ~~an~~ optional~~,~~ exploratory ~~CBA~~cytokine profiling to assess inflammatory biomarkers and plasma cytokine levels. Inpatient observation can be extended and additional blood samples can be collected if deemed necessary at the discretion of the Investigator and Medical Monitor.	1, 12
12.5.1/Once per Week Weeks 1-26	• Liver Tests (refer to Table 9.7.8.3.1) ○ ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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	6, 8, 10, 12

Section No./Title	Revision	Rationale
	○ Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor) ~~• FVIII protein assay~~ • Exploratory CK18 ~~and Grp78~~ assessment	
12.5.2/Day 8	On Day 8, the following procedures will be performed, in addition to the weekly assessments required in Section 12.5.1: • Complement Panel and Exploratory Cytokine Profiling	12
12.5.4/Weeks 2, 4, 8, 12, 16, 20, 24, 26	At Weeks 2, 4, 8, 12, 16, 20, 24, and 26, the following procedure will be performed: • Complement Panel and Exploratory Cytokine Profiling	12
12.5.6/Weeks 4, 8, 12, 16, 20, 24, 26	At Weeks 4, 8, 12, 16, 20, 24, and 26, the following procedures will be performed: • hFVIII protein assay	8
~~12.5.13/Weeks 16, 20, 26~~	~~At Weeks 16, 20, and 26, the following procedure will be performed:~~ ~~• TGA Assay~~	7
12.6.1/Each Visit Weeks 27-52	• Liver Tests (refer to Table 9.7.8.3.1) ○ ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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 ○ Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor) ~~• FVIII protein assay~~ • Exploratory CK18 ~~and Grp78~~ assessment	6, 8, 10, 12
12.6.5/Weeks 32, 36, 40, 44, 48, 52	At Weeks 32, 36, 40, 44, 48, and 52, the following procedure will be performed: • hFVIII protein assay	8
12.6.6/Weeks 32, 36, 44, 52	At Weeks 32, 36, 44, and 52, the following procedures will be performed:	7

Section No./Title	Revision	Rationale
	• ~~TGA Assay~~	
12.6.7/Week 36 and 52	At Weeks 36 and 52, the following procedures will be performed: • Complement Panel and Exploratory Cytokine Profiling	12
12.6.8/Week 52	At Week 52, the following procedure will be performed: • Liver ultrasound o Additional liver ultrasounds may be performed prior to Week 52 at the discretion of the Investigator	2
12.7.1/Every 4-6 Weeks Years 2-5	During Years 2 (every 4 weeks ± 2 weeks) or Years 3-5 (every 6 weeks ± 2 weeks), the following procedures will be performed: • Liver Tests (refer to Table 9.7.8.3.1) o ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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 o Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor) • FVIII protein assay • Exploratory CK18 ~~and Grp78~~ assessment	6, 8, 10, 12
12.7.2/Years 2-5 Every 12 Weeks or End of Year Visits	At the every 12 week and End of Year visits, the following procedures will be performed: • Physical examination o Complete physical examination will be performed at the End of Year visits~~;~~ (genitourinary examination may be deferred); brief physical examination may be performed at other visits. • Liver Tests (refer to Table 9.7.8.3.1) o ~~LTs~~LT assessment may be ~~monitored~~checked more ~~or less~~ frequently ~~(and in particular~~ when ALT values are > ULN or ≥ 1.5x baseline value~~)~~ or based ~~on~~upon 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.~~.	2, 6, 8, 10. 12

Section No./Title	Revision	Rationale
	• FVIII Assays o Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor) • ~~FVIII~~hFVIII protein assay • AAV5 TI Assay (at End of Year ~~visits~~5 visit only) • Exploratory CK18 ~~and Grp78~~ assessment • ~~TGA Assay~~Liver ultrasound (at End of Year visits only) o Additional liver ultrasounds may be performed at interim timepoints (ie, between the End of Year visits) at the discretion of the investigator	
12.8/Early Termination Visit	At the ETV, as many of the following assessments as possible should be done: • FVIII Assays o Chromogenic Nijmegen-Bethesda Assay for hFVIII inhibitor level (assay will be tested as deemed necessary by the Sponsor) • ~~FVIII~~hFVIII protein assay • Exploratory CK18 ~~and Grp78~~ assessment • ~~TGA Assay~~	7, 8, 10, 12
14.3/Secondary Efficay Endpoints	The analyses of the secondary efficacy endpoints will be descriptive. Mean and associated 95% confidence interval will be provided for the following secondary endpoints, where the baseline value will be derived from the data in the approximately 12-month period prior to BMN 270 infusion: • For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized utilization (IU/kg/year) of exogenous FVIII replacement therapy ~~during Weeks~~from Week 5 ~~52~~ post -BMN 270 infusion to last visit by data cutoff (for Week 52 analysis); and separately, for subjects receiving ~~FVIII~~prior emicizumab prophylaxis ~~during the 12 months prior to study entry, or,~~ change from baseline in the annualized utilization (mg/kg/year) of emicizumab ~~during~~from Week 27 ~~to Week 52~~ post -BMN 270 infusion ~~for subjects receiving prior emicizumab prophylaxis~~to last visit by data cutoff (for Week 52 analysis)	11, 12

Section No./Title	Revision	Rationale
	• For subjects receiving FVIII prophylaxis prior to study entry, change from baseline in the annualized infusion rate (number/year) of exogenous FVIII replacement therapy ~~during Weeks~~from Week 5 ~~52~~ post ~~-~~BMN 270 infusion~~,~~ to last visit by data cutoff (for Week 52 analysis); and separately for subjects receiving ~~FVIII~~prior emicizumab prophylaxis ~~during the 12 months prior to study entry, or,~~ change from baseline in the annualized utilization (mg/kg/year) of emicizumab ~~during~~from Week 27 ~~to Week 52~~ post ~~-~~BMN 270 to last visit by data cutoff (for Week 52 analysis) infusion ~~for subjects receiving prior emicizumab prophylaxis~~ • Change from baseline in the annualized number of bleeding episodes (number/year) requiring exogenous FVIII replacement treatment ~~during Weeks~~from Week 5 ~~52~~ post-BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior FVIII prophylaxis, or ~~Weeks~~ from Week 27 ~~52~~ post~~-~~BMN 270 infusion to last visit by data cutoff (for Week 52 analysis) for subjects receiving prior emicizumab prophylaxis from baseline	
14.8/Determination of Sample Size	Approximately 20 subjects may be dosed in the study, including at least 16 subjects who are AAV5 antibody-negative and up to 25% of the total number of subjects ~~who have~~with an AAV5 antibody titer that is detectable but below the minimum required dilution (< 20) at Screening.	12
14.9/Analysis Populations	The AAV MRD population (ie, subjects with an AAV5 antibody titer detectable but below the minimum required dilution) will be used for exploratory efficacy analysis on FVIII activity, as measured by chromogenic substrate assay, during Weeks 49-52 post BMN 270 infusion.	12
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. When in person site monitoring or source data verification cannot be conducted, remote site monitoring and/or source data verification will be conducted where allowed by country and local health authorities and ECs/IRBs.	12
21/References	~~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.~~ United States Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2019. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf (last accessed 17 May 2021).	4, 12